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INVESTIGATION OF SELECTED POTENTIAL ENVIRONMENTAL CONTAMINANTS:

FORMALDEHYDE

FINAL REPORT

REPRODUCED BY
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U. S. DEPARTMENT OF COMMERCE
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ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF TOXIC SUBSTANCES
WASHINGTON, D.C. 20460

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16. ABSTRACT

This report reviews the potential environmental hazards of formaldehyde resulting from its manufacture, use, production from combustion processes and inadvertent production in the environment. Nascent sources of formaldehyde, such as paraformaldehyde, trioxane and hexamethylenetetramine, are also reviewed. The major source of atmospheric discharge of formaldehyde is combustion processes, specifically from automobile emissions. Formaldehyde is also a product of atmospheric photooxidation of hydrocarbons emitted from automobiles. Photochemical degradation of formaldehyde also occurs in the atmosphere. Formaldehyde is a mutagen is lower animals such as Drosophila and bacteria. This property is the basis of its use as a fumigant. Even though formaldehyde is a strong alkylating agent, information to date indicates that it is not mutagenic or carcinogenic in mammals, probably due to the mammalian body's ability to repair this type of nucleic acid damage. Formaldehyde is an allergen. It is also highly toxic in low concentrations causing eye and lung damage and affecting the central nervous system. However, formaldehyde is also a metabolite in biological systems and can be efficiently metabolized to formic acid, carbon dioxide and water, or utilized in the one carbon pool.

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INVESTIGATION OF SELECTED POTENTIAL ENVIRONMENTAL CONTAMINANTS: FORMALDEHYDE

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August 1976
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EXECUTIVE SUMMARY

Formaldehyde is a high volume chemical in the United States. Production levels are currently around 6000 million pounds annually on a 37% basis. This level is predicted to increase to 7600 million pounds in 1979. Formaldehyde is manufactured in the United States by two processes: silver catalyst and metal oxide catalyst. The silver catalyst process has less emissions, if incineration of the absorber emissions to produce steam is employed. The metal oxide process produces a fuel-lean absorber gas which is normally vented into the atmosphere. This stream represents the major source of formaldehyde manufacturing emissions. The major use of formaldehyde is in the production of phenolic, urea and melamine resins. The production and use of these resins generates contamination problems (primarily water) in localized areas such as the Pacific Northwest and the Northeast.

Although formaldehyde manufacture and resins production contribute significantly to localized releases, they are not the main source of environmental contamination from formaldehyde. The major source of environmental contamiantion is combustion processes, primarily automobile emissions. Automobiles in the United States are estimated to emit 610 x 10^6 lbs of formaldehyde each year. In addition to being the major formaldehyde emitter, automobiles also emit hydrocarbons which are photochemically converted to formaldehyde in the atmosphere. Formaldehyde is degraded in the environment by photochemical processes in air, and biologically by certain bacteria in water and soil. Thus, formaldehyde does not pose a bioaccumulation or magnification problem.

Formaldehyde has long been recognized as a protoplasmic poison, mainly due to its ability to coagulate proteins. Dermatological reactions from exposure are well known. Inhalation of high concentrations of formaldehyde can cause severe lung damage which can lead to pulmonary collapse and death. Liver and renal damage are also observed. In airborne subacute exposures, lung and eye irritation are observed, as well as central nervous system depression. Inhalation of concentrations as low as 1 ppm have been reported to produce central nervous system responses. These findings, if verified, indicate that the current TLV of 2 ppm may be too high. Ingestion of formaldehyde causes severe damage to the gastrointestinal tract. Once formaldehyde is absorbed into the body, either through the gastrointestinal tract or the lungs, it is quickly oxidized to formic acid or reacts with body proteins or tetrahydrofolic acid. Several enzymes are available to catalyze this oxidation. These enzymes are mainly located in the erythrocytes and the liver. The formic acid thus formed can be further oxidized to CO_2 and water, or enter basic metabolic processes.

In contrast, hexamethylenetetramine is relatively innocuous. This compound passes through the body unchanged and is eliminated in the urine. If the urine is sufficiently acid, hexamethylenetetramine hydrolyzes to ammonia and formaldehyde. This hydrolysis is the basis for its use as a urinary antiseptic.

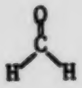
Formaldehyde is a known mutagen in certain bacterial strains and drosphila. However, no substantive evidence has been presented to date to show that either formaldehyde or hexamethylenetetramine induces mutagenic, carcinogenic, or teratogenic responses in humans or mammals.

I. INTRODUCTION

Formaldehyde is produced in large quantities in the United States for use in the production of resins, as a starting material for chemical synthesis, as a fumigant, and as a tissue preservative. Due to its wide usage, the Environmental Protection Agency, Office of Toxic Substances, has initiated an investigation into the environmental contamination potential of this compound. This report presents the results of a survey and evaluation of the literature on formaldehyde and nascent formaldehyde, including paraformaldehyde, trioxane and hexamethylenetetramine. The survey covers the period from 1954 to the present (June, 1976), although older information has been included for areas where no recent work has been performed. The major topics covered in this report are commercial formaldehyde manufacture and production statistics, inadvertent production by other man-made sources and in the environment; environmental fate; human, animal and plant toxicology, carcinogenicity, and mutagenicity; and current handling practices and regulations.

II. STRUCTURE AND PROPERTIES

Pure, dry formaldehyde is a colorless gas possessing a pungent odor and an irritating effect on the mucous membranes of the body. In the pure, dry form, formaldehyde exists as a monomer. The monomer is a planar molecule possessing the following structure:



The C-O bond length is 1.230 ± 0.017 Å and the C-H bonds are 1.060 ± 0.017 Å in length. The HCH angle is 1.258 ± 7° (Weast, 1975). The physical properties of monomeric formaldehyde are listed in Table 1.

TABLE 1. Properties of Monomeric Formaldehyde (Weast, 1975; Walker, 1975)

Formula	HCHO
IUC Name	Methanal
Common Names	formaldehyde, oxomethane, methylene oxide, oxymethylene, methyl aldehyde, formic anhydride
CAS Registry Number	50-00-0
Wiswesser Line Notation	VHH
Color	Colorless gas
Odor	Pungent
M.P., °C	-92
B.P., °C	-19.2
Density at -20°C, g/ml	0.8153

Density, at -80°C, g/ml		0.9151
Heat of Vaporization, kcal/g		5.570
Heat of Combustion, kcal/g		4.47
Flammability limits in air (volume %)	lower	7
	upper	72

Monomeric formaldehyde readily polymerizes, especially in the presence of impurities, to yield various species of polymers. For this reason, commercial formaldehyde is almost always found in solution form or in the form of a solid polymer which can be depolymerized to yield CH_2O as the reacting species.

A. FORMALDEHYDE SOLUTIONS

Formaldehyde solutions can be categorized as either true solutions or solutions in which formaldehyde is in chemical combination with the solvent. True formaldehyde solutions are found only with non-polar solvents, such as toluene, ether, chloroform and ethyl acetate. These solutions are not available commercially. The latter type of solutions occur with polar solvents, such as water and alcohols.

Aqueous solutions are the common commercial form of formaldehyde encountered in both the United States and the European continent, although alcoholic solutions are also available. Aqueous commercial formaldehyde solutions, often called formalin, range in formaldehyde content from 37 to 50 percent by weight. These solutions are available in both inhibited and uninhibited forms. The inhibited formaldehyde solutions contain 6.0 to 15.0 weight percent of a stabilizer, usually methanol. The stabilizers are added to the formaldehyde solutions to inhibit solid polymer formation. According to Walker (1975), the action of solution stabilizers in the prevention of polymer formation is due to the formation of hemiacetals which exist in equilibrium with the hydrated formaldehyde in solution. This equilibrium can be shown by:

$$\underset{\substack{\text{hydrated}\\\text{formaldehyde}\\\text{(methylene glycol)}}}{\mathrm{HO{-}CH_2{-}OH}} + \underset{\text{methanol}}{\mathrm{CH_3OH}} \rightleftharpoons \underset{\substack{\text{formaldehyde}\\\text{hemiformal}}}{\mathrm{HO{-}CH_2{-}OCH_3}} + \underset{\text{water}}{\mathrm{H_2O}} \qquad (1)$$

$$\underset{\substack{\text{diformaldehyde}\\\text{monohydrate}\\\text{(dioxymethylene glycol)}}}{\mathrm{HO{-}CH_2{-}O{-}CH_2{-}OH}} + \underset{\text{methanol}}{\mathrm{CH_3OH}} \rightleftharpoons \underset{\substack{\text{diformaldehyde}\\\text{hemiformal}}}{\mathrm{HO{-}CH_2{-}O{-}CH_2{-}OCH_3}} + \underset{\text{water}}{\mathrm{H_2O}} \qquad (2)$$

Uninhibited formalin solutions also contain methanol, although the percentage is small as shown in Table 2.

TABLE 2. Representative Analysis for 37% Commercial Formalin (Walker, 1975)

Component	Uninhibited	Inhibited
HCHO, wt %	37.0 - 37.5	37.0 - 37.5
CH_3OH, wt %	0.3 - 1.5	6.0 - 15.0
Acidity (Wt % HCOOH)	0.01 - 0.05	0.01 - 0.03
Iron (ppm)	0.5 - 0.8 max	0.5 - 0.8 max
Aluminum (ppm)	3 max	3 max
Copper (ppm)	1 max	1 max
pH	2.8 - 4.0	2.8 - 4.0

The uninhibited solutions are usually made for immediate use. To prevent polymerization, they must be stored at elevated temperatures. The minimum temperature necessary for storage is a function of formaldehyde concentration, increasing with increasing concentration.

The physical properties of formaldehyde solutions are a function of the weight percent of formaldehyde and stabilizer present. Properties for specific commercial solutions are presented in Table 3.

TABLE 3. Physical Properties of Commercial Formaldehyde Solutions (Walker,1975)

HCHO, wt %	37	37	37	45	50
CH_3OH, wt %	1	5	10	1	1
b.p., °C	98.9	97.8	97.8	99.4	99.4
Density at 18°C, g/ml	1.113	1.101	1.089	1.135	1.150
Flash point, °C (closed cup)	85.0	77.2	63.9	80.6	79.4
Approx. specific heat (cal/g/°C)	0.8	0.8	0.8	0.6	0.6

Alcoholic solutions of formaldehyde are also available commercially for processes where high alcohol-low water content is desirable. These solutions, called Formcels*, are made with methanol, n-propanol, n-butanol and iso-butanol. Typical properties of methanol and n-butanol Formcels are listed in Table 4.

---

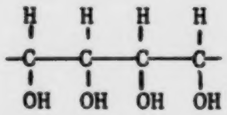
*Registered trademark of Celanese Corporation

TABLE 4. Physical Properties of Commercial Formcel Solutions (Chemical Week, Oct. 1975)

	Methanol	n-butanol
HCHO, wt %	55.0 ± 0.5	40.0 ± 0.5
Alcohol, wt %	34.0 - 35.0	52 - 53
Water, wt %	10.0 - 11.0	6.5 - 7.5
Iron (ppm)	0.5 max	0.5 max
Acidity, wt % HCOOH	0.04	0.03
b.p., °C	102	107
Specific gravity 25/25°C	1.064	0.973
Flash point, °C	44.4 (closed cup)	74.4 (open cup)

B. FORMALDEHYDE POLYMERS

The ease with which monomeric formaldehyde polymerizes allows the formation of a wide variety of stable and commercially useful polymers. Formaldehyde polymers can be initially classifed into two fundamentally different forms: the polyoxymethylenes, and the polyhydroxyaldehydes. The polyhydroxyaldehydes have the following general structure:



$$-\overset{H}{\underset{OH}{C}}-\overset{H}{\underset{OH}{C}}-\overset{H}{\underset{OH}{C}}-\overset{H}{\underset{OH}{C}}-$$

These compounds are formed by aldol-type condensations, the predominant end products of which are sugars.

The polyoxymethylene polymers possess the general chemical structure shown below:

$$-CH_2-O-CH_2-O-CH_2-O-.$$

These compounds are often considered as the only true formaldehyde polymers. The polyoxymethylenes can be classified into linear and cyclic forms as shown in Figure 1.

1. Linear Polyoxymethylene Polymers

The linear polyoxymethylenes can be further classified on the basis of chemical behavior, type of end group attached to the molecule, and molecular weight, as illustrated in Figure 1. Walker (1975) notes that the classification is simply a matter of convenience.

The polyoxymethylene glycols have the following structure: $HO(CH_2O)_n \cdot H$. As illustrated in Table 5, the properties of these compounds are highly dependent upon their degree of polymerization and molecular weight. The polyoxymethylene glycols are of considerable commerical importance. This importance is due to their ability to act as a solid source of formaldehyde. Upon vaporization, they depolymerize to yield monomeric formaldehyde gas.

a. Oligo-oxymethylene Glycols

The lower molecular weight oligo-oxymethylene glycols are usually formed as the result of cooling aqueous formaldehyde solutions which causes the polymers to precipitate. The rate of cooling and the concentration of the solution determine the point at which precipitation occurs. In general, a mixture of polymers with different degrees of polymerization, n, results. However, many of these lower molecular weight oligo-oxymethyelene glycols have been isolated and studied (Staudinger, 1932).

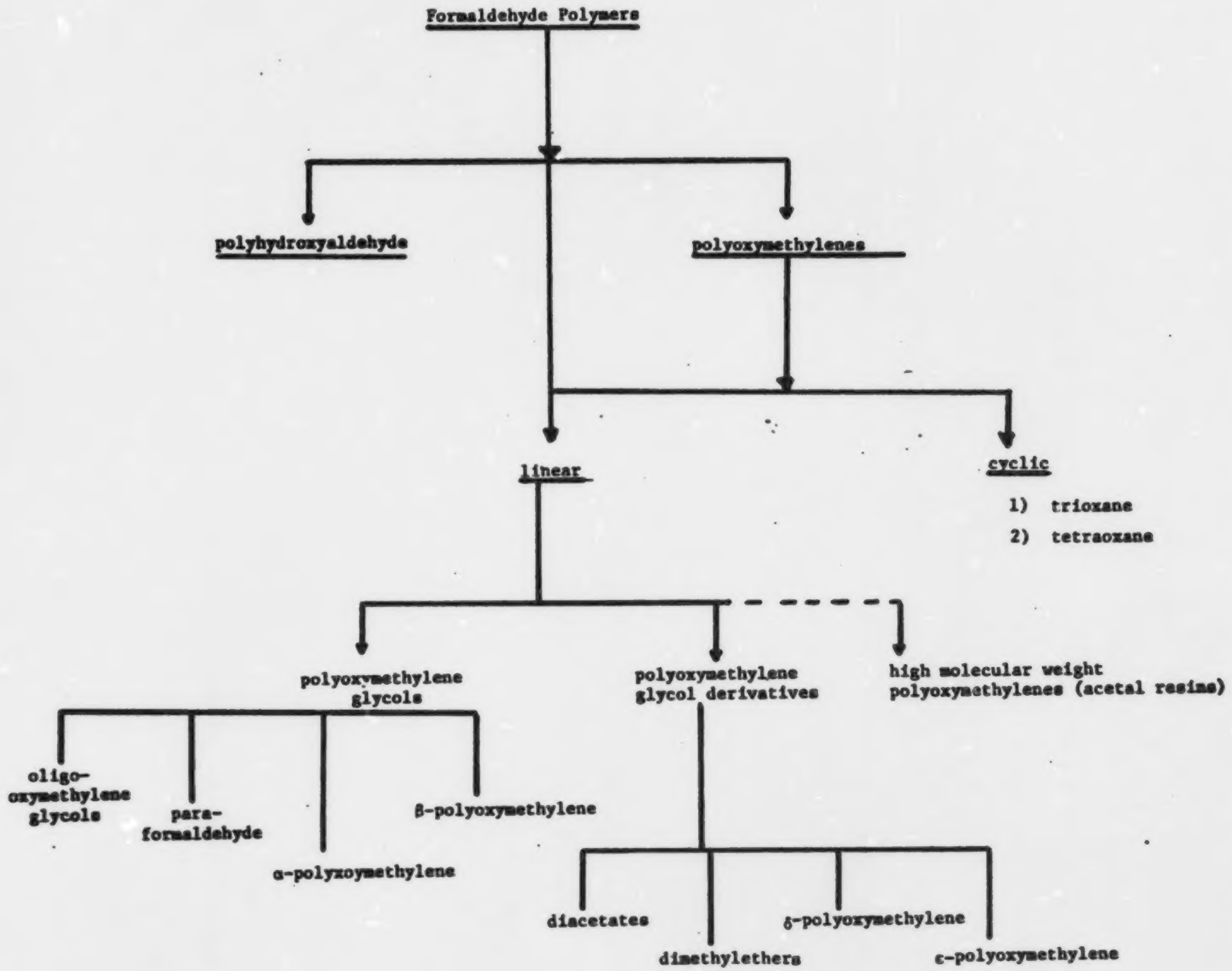

Formaldehyde Polymers
polyhydroxyaldehyde
polyoxymethylenes
linear
cyclic
1) trioxane
2) tetraoxane
polyoxymethylene glycols
polyoxymethylene glycol derivatives
high molecular weight polyoxymethylenes (acetal resins)
oligo-oxymethylene glycols
para-formaldehyde
α-polyxoymethylene
β-polyoxymethylene
diacetates
dimethylethers
δ-polyoxymethylene
ε-polyoxymethylene

Figure 1. Classifications of Formaldehyde Polymers

TABLE 5. Structure and Properties of Formaldehyde Polymers
(Walker, 1975)

	Type Formula	Range of Polymerization n	% CH_2O wt	Melting Range °C	Solubility			
					H_2O	Acetone	Diluted Base	Diluted Acid
Linear Polymers								
lower polyoxymethylene glycols	$HO(CH_2O)_n \cdot H$	2-8	77-98	80-120	vs	s-i	vs	vs
paraformaldehyde	$HO(CH_2O)_n \cdot H$	6-100	91-99	120-170	ds	s-i	s	s
α-polyoxymethylene	$HO(CH_2O)_n \cdot H$	100-300	99.0-99.9	170-180	vds	i	s	s
β-polyoxymethylene	$HO(CH_2\ )_n \cdot H$ + trace H_2SO_4	100-300	98-99	165-170	vds	i	ds	ds
Polyoxymethylene Glycol Derivative								
polyoxymethylene diacetates	$CH_3CO \cdot O(CH_2O)_n \cdot COCH_3$	2-200	37-93	<165	i for n >10	i	ds	ds
lower polyoxymethylene dimethyl ethers	$CH_3O \cdot (CH_2O)_n \cdot CH_3$	2-200	72-93	175	-	i for n >15	i for n >15	ds
γ-polyoxymethylene	$CH_3O \cdot (CH_2O)_n \cdot CH_3$	200-300	93-99	160-~180	i	i	i	ds
δ-polyoxymethylene	$CH_3O \cdot (CH_2O)_n CH_2CH(OH)OCH_3$	>100	96-97	150-170	i	i	i	ds
ε-polyoxymethylene	$(CH_2O)_n$(?)	>100	99.7-99.9	195-200	i	i	-	-
High Molecular Weight Polyoxymethylene	$HO \cdot (CH_2O)_n \cdot H$	500-5000	99.9-100	170-185	i	i	vds	vds
Cyclic Polymers								
trioxane	$(CH_2O)_3$	3	100	61-62	s	s	s	s
tetraoxane	$(CH_2O)_4$	4	100	112	s	s	s	s

Key

s = soluble
vs = very soluble
ds = difficultly soluble
vds = very difficultly soluble
i = insoluble

b. Paraformaldehyde

Paraformaldehyde is loosely defined as a mixture of polyoxymethylene glycols containing 90 to 99 percent formaldehyde. It is formed from the condensation of methylene glycols. The following equation is generally agreed to be the reaction sequence:

$$n\ CH_2(OH)_2 \longrightarrow (CH_2O)_n \cdot H_2O + (n-1)H_2O. \tag{3}$$

Paraformaldehyde is produced commercially for use in processes where water is undesirable. The structure and physical properties of paraformaldehyde are shown in Table 6.

TABLE 6. Composition and Physical Properties of Commercial Paraformaldehyde (Walker, 1975; Chemical Week, Oct. 1975)

Formula	$HO(CH_2O)_n \cdot H$ (n=6-100)
Common Names	paraform paraformaldehyde
CAS Registry Number	---
Wiswesser Line Notation	---
Color	Colorless, solid
Odor	Pungent, that of formaldehyde
Polymer, wt %	91.0-97.0
Water, wt%	5.0 - 9.0 max
Iron (ppm)	2

Acidity as HCOOH, wt %		0.03
m.p., °C		120-170
b.p., °C		decomposes
Specific gravity at 15°C g/ml		1.46
Flash point, °C (closed cup)		71
(open cup)		93
Autoignition temperature, °C		410
Flammability limits in air, wt %	lower	7.0
	upper	73.0

Paraformaldehyde serves as a source of monomeric formaldehyde by the "unzipping" action of the polymer. This process is thought to occur in the following manner (Walker, 1975):

$$-CH_2-O-CH_2-O-CH_2OH \longrightarrow -CH_2-O-CH_2-OH + HCHO \qquad (4)$$

This ability to serve as a solid source of relatively pure monomeric formaldehyde has promoted paraformaldedhyde to a place of commercial importance. One of the most interesting facets of the behavior of paraformaldehyde is that at ordinary temperatures it vaporizes to monomeric formaldehyde. This behavior has been extensively characterized (Nordgren, 1939).

c. α- and β-Polyoxymethylenes

The next homologues of the linear polyoxymethylene series are the alpha and beta polyoxymethylenes. The α-polyoxymethylenes are similar in structure and properties to paraformaldehyde, but contain a higher formaldehyde content. The β-polyoxymethylenes are obtained upon addition of sulfuric acid to formalin solutions, followed by cooling. There is disagreement as to whether the acid is chemically combined with the product or not. This polymer is very stable, and may even be sublimed without gross decomposition.

d. High Molecular Weight Polyoxymethylene

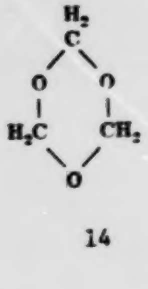
High molecular weight polyoxymethylenes range from unstable materials to the highly stable acetal resins. These resins possess excellent mechanical properties, as well as a high degree of thermal stability and toughness retention. The properties of the final polymer are determined by the method of preparation and the purity of the formaldehyde monomeric starting material. The acetal resins represent an end use of formaldehyde and will be discussed in detail in Section III-B, page 49.

e. Polyoxymethylene Derivatives

Several derivatives of polyoxymethylene are possible. The general structures and properties of these polymers are given in Table 5. Studies of these polymers have increased the understanding of other polyoxymethylenes. However, these derivatives are not of commercial importance. and would not contribute to the environmental contamination potential of formaldehyde.

2. Cyclic Polymers

The cyclic trimer of formaldehyde is trioxane or α-trioxymethylene. Because of its commercial value in acetal resin formation, trioxane has been extensively characterized. The structure of trioxane, shown below, is that of a non-planar ring.



Its physical properties are delineated in Table 7.

TABLE 7. Composition and Physical Properties of Trioxane (Walker, 1975; Chemical Week, Oct. 1975)

Formula	$(CH_2)_3O_3$
Common Names	Metaformaldehyde, aldeform, triformol, s-trioxane, sym-trioxane, 1,3,5-trioxane, α-trioxymethylene, marvosan
CAS Registry number	110-88-33
Wiswesser Line Notation	T60 CO E OTJ
Color	Colorless crystal
Odor	chloroform-like
Purity, wt %	99.0 min
Water, wt %	0.3 - 1.0 max
Iron (ppm)	2
Acidity as HCOOH, wt %	0.02
m.p., °C	61-62
b.p., °C	114.4
Specific gravity at 65°C, g/ml	1.17
Flash point, °C (open cup)	45

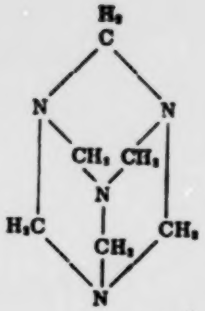
Trioxane differs from the linear polyoxymethylene polymers in many ways. These differences are manifested in the physical and chemical properties of the trimer. One of the most obvious differences to the casual observer is the odor. Whereas the linear polyoxymethylene polymers possess the characteristic odor of formaldehyde due to depolymerization, trioxane has a pleasant, chloroform-like odor. This difference in odor is due to the lack of depolymerization of trioxane to formaldehyde under ordinary conditions. In fact, the trimer can be boiled without decomposition.

Trioxane is soluble without decomposition in several common organic solvents, including alcohols, ketones, organic acids, ethers, esters, phenols, aromatic hydrocarbons, and chlorinated hydrocarbons (Walker, 1975). It is also soluble in water, from which it can be crystallized. The solubility ranges from 17.2g /100 cc at 18°C to infinite in hot water. Trioxane is also stable in alkaline solutions. However, in aqueous solutions of strong acids, such as sulfuric acid, trioxane is depolymerized to yield formaldehyde. This reaction has been extensively studied for industrial application, where a controlled rate of formaldehyde production is necessary for a reaction.

Tetraoxane is the little known tetramer of formaldehyde whose chemical formula has been determined to be $(CH_2O)_4$. The melting point has been determined to be 112°C, but no data was found on other physical properties or structure. Tetraoxane is not produced commercially.

C. HEXAMETHYLENETETRAMINE

Hexamethylenetetramine is a cyclic compound formed by the reaction of monomeric gaseous formaldehyde with ammonia. Due to its commercial importance in the resin and munitions manufacturing industries, its properties and structure have been extensively studied. The structure of hexamethylenetetramine was first proposed in 1895 by Duden and Scharff (Walker, 1975) to be:



Although several other structures have been proposed, x-ray (Schomaker and Shaffer, 1947; Shaffer, 1947) and Raman spectra (Bai, 1944) support the above structure. Bond lengths determined from x-ray diffraction studies are reported to be 1.48 ± 0.01 Å in the gaseous phase and 1.45 ± 0.01 Å in the crystalline phase. The C-N-C and the N-C-N angles are both 109.5 ± 1° for the gaseous phase. In the crystalline phase, the C-N-C and the N-C-N angles are 107 and 113°30', respectively (Schomaker and Shaffer, 1947).

The physical properties of hexamethylenetetramine are presented in Table 8.

TABLE 8. Composition and Physical Properties of Commercial Hexamethylenetetramine (Walker, 1975; CHRIS, 1974)

Formula	$(CH_2)_6N_4$
IUC Name	1,3,5,7-tetraazatricyclo-(3.3.1.1.)decane
Common Names	aceto HMT, aminoform, ammoform, cystogen, formen, HEXA, hexaform, hexamethyleneamine, hexamine, methenamine, preparation AF, resotropin, 1,3,5,7-tetrazoadamantane, urotropine

CAS Registry Number	100-97-0
Wiswesser Line Notation	T66 B6 A B- C 1B J BN DN FN HNTJ
Color	Colorless
Odor	Odorless to mild ammonia
Purity, wt %	99$^+$
m.p., °C	does not melt
b.p., °C	sublimes with slight decomposition
Specific gravity at 20°C, g/ml	1.35
Flash point, °C (closed cup)	250

Hexamethylenetetramine is slightly soluble in a variety of organic solvents as illustrated in Table 9.

TABLE 9. Solubility of Hexamethylenetetramine (Seidell, 1928)

		Solubility g/100cc solvent
Solvent	Room Temperature	Elevated Temp.
petroleum ether	insoluble	insoluble
ethyl ether	0.06	0.38
trichloroethylene	0.11	-
xylene	0.14	-
carbon disulfide	0.17	-
benzene	0.23	-
acetone	0.65	-
carbon tetrachloride	0.85	-
absolute ethanol	2.89	-
methanol	7.25	11.93
chloroform	13.40	14.84

Water dissolves hexamethylenetetramine with the evolution of heat. The solubility is unusual in that it tends to decrease with increasing temperature. Hydrolysis does occur, the rate of which is highly dependent upon pH and temperature.

D. CHEMISTRY

The unique chemical structure of formaldehyde is responsible for its high degree of chemical reactivity in comparison with other carbonyl compounds. This structural uniqueness is due to the attachment of the carbonyl directly to two hydrogens. Thus, the chemical stability associated with enol-keto tautomerism in the higher aldehydes is lacking in formaldehyde.

Because of its high chemical reactivity and good thermal stability, formaldehyde is used as a reactant in numerous commercial processes to synthesize a wide variety of products. Basically these reactions fall into three categories:

- oxidation-reduction reactions.
- addition or condensation reactions with organics and inorganics.
- self polymerization reactions.

A general description of these reactions as applied to formaldehyde is represented in Figure 2, and described below. Specific reactions involved in industrial use of formaldehyde are presented in Section III-B, page 44. The environmental chemistry of formaldehyde is discussed in Section IV-A, page 103.

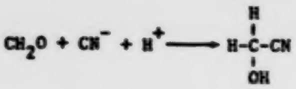
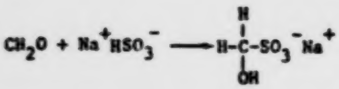
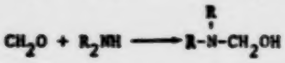
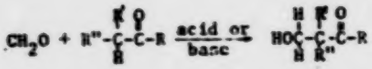
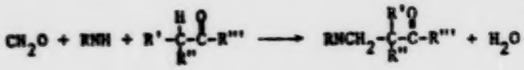
Formaldehyde is a strong reducing agent in basic solution, itself being oxidized to formic acid. One use of its reducing power is in the

Figure 2. General Reactions of Formaldehyde

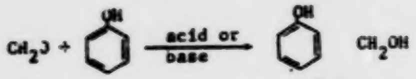
Oxidation - Reduction

A.	$CH_2O + 3OH^- \xrightarrow[1.14V]{} HCOO^- + 2H_2O + 2e^-$	
B.	$CH_2O + 2Ag(NH_3)_2 + 3OH^- \longrightarrow 2Ag + HCOO^- + 4NH_3 + 2H_2O + 2e^-$	Tollins Reaction
C.	$2CH_2O + OH^- \longrightarrow HCOO^- + CH_3OH$	Cannizzaro Reaction
D.	$CH_2O + RCHO + OH^- \longrightarrow HCOO^- + RCH_2OH$	Crossed Cannizzaro Reaction

Addition

E.	 $CH_2O + CN^- + H^+ \longrightarrow H\text{-}\overset{H}{\underset{OH}{C}}\text{-}CN$	Cyanohydrin Formation
F.	 $CH_2O + Na^+HSO_3^- \longrightarrow H\text{-}\overset{H}{\underset{OH}{C}}\text{-}SO_3^-Na^+$	Addition of Bisulfite
G.	$2CH_2O + 2HCl \longrightarrow ClCH_2OCH_2Cl + H_2O$	Bis(chloromethyl)ether formation
H.	$6CH_2O + 4NH_3 \longrightarrow C_6N_4H_{12} + 6H_2O$	Hexamethylenetetramine formation
I.	$CH_2O + RNH_2 \longrightarrow R\text{-}NHCH_2OH$	Condensation with amines
J.	 $CH_2O + R_2NH \longrightarrow R\text{-}\overset{R}{N}\text{-}CH_2OH$	Condensation with amines
K.	$CH_2O + RCONH_2 \longrightarrow RCONHCH_2OH \xrightarrow{CH_2O} RCON(CH_2OH)_2$	Condensation with amides
L.	$CH_2O + ROH \xrightarrow{H^+} RO\text{-}CH_2OH \xrightarrow[ROH]{H^+} ROCH_2\text{-}OR$	Acetal Formation
M.	 $CH_2O + R''\text{-}\overset{R'}{\underset{H}{C}}\text{-}\overset{O}{C}\text{-}R \xrightarrow[base]{acid\ or} HO\overset{H}{\underset{H}{C}}\text{-}\overset{R'}{\underset{R''}{C}}\text{-}\overset{O}{C}\text{-}R$	Aldol Condensation
N.	 $CH_2O + RNH + R'\text{-}\overset{H}{\underset{R''}{C}}\text{-}\overset{O}{C}\text{-}R''' \longrightarrow RNCH_2\text{-}\overset{R'}{\underset{R''}{C}}\text{-}\overset{O}{C}\text{-}R''' + H_2O$	Mannich Reaction

Reaction with Active H

O.		Methylol Formation
P.	$CH_2O + RMgX \longrightarrow RCH_2(OMgX) \xrightarrow{H_2O} RCH_2OH + XMgOH$	Grignard
Q.	$H_2C{=}O + H_2O \rightleftharpoons H_2C(OH)_2$ $nH_2C(OH)_2 \rightleftharpoons HO\cdot(CH_2O)_n\cdot H + (n-1)H_2O$	Formation of polyoxymethylene

production of silver mirrors. This reaction is carried out in an ammoniacal silver solution. The silver is reduced, plating the desired surface with a mirror coating (Reaction B). The Cannizzaro reactions also involve an oxidation of formaldehyde. This reaction is responsible for the formation of formic acid in formalin solutions upon aging. The crossed-Cannizzaro reaction is useful in reducing other aldehydes to the corresponding alcohol.

Important addition reactions include methylol formation, aldol condensations, condensation with ammonia, etc. Aldol condensations are important in the synthesis of β-hydroxycarbonyl compounds which can be used in further synthesis, e.g., pentaerythritol production. Methylol derivatives are highly reactive species which can be polymerized to yield methylene or ether bridges, e.g., phenolic resins. Condensation of formaldehyde with ammonia yields hexamethylenetetramine which undergoes many reactions including decomposition into formaldehyde and ammonia, and nitramine formation upon nitration. The polymerization reactions and their products were previously discussed in Section II-B, page 8.

III. ENVIRONMENTAL EXPOSURE FACTORS

A. PRODUCTION AND CONSUMPTION

1. Quantity Produced

Formaldehyde is a high volume commercial chemical which is available in several different forms to fit the users' needs:

- aqueous solutions varying in formaldehyde concentration from 37 to 50 weight percent and methanol concentration from 0.3 to 15.0 weight percent.
- alcoholic solutions varying in formaldehyde concentrations and type and concentration of alcohol present.
- paraformaldehyde.
- trioxane.
- hexamethylenetetramine.

The production figures quoted for formaldehyde are almost universally normalized to a 37 weight percent formalin solution. There are two reasons for this normalization:

- The basic manufacturing process is not influenced by the final product; only the final compounding steps serve to vary the product form.
- The amount and type of final product produced at any facility is highly dependent upon fluctuating captive needs and customer requirements. The 37 percent figure includes all aqueous and alcoholic solutions, paraformaldehyde and trioxane.

Hexamethylenetetramine is considered as a formaldehyde consumer and is thus reported separately. However, the formaldehyde used to produce hexamethylenetetramine is included in the 37% production figure.

Production figures for formaldehyde and hexamethylenetetramine are presented in Table 10 and Figures 3 and 4.

TABLE 10. Formaldehyde (37% Bases) and Hexamethylenetetramine Production (U. S. Tarriff Commission; Chemical Marketing Reporter, 1975; Predicasts, 1975)

Production Levels, Millions of Pounds

Year	Formaldehyde	Hexamethylenetetramine
1960	1872	26.1
1961	1752	28.2
1962	2398	36.4
1963	2537	41.3
1964	2840	42.8
1965	3107	49.3
1966	3713	78.3
1967	3707	84.3
1968	4305	96.8
1969	4398	97.0
1970	4427	76.6
1971	4522	47.4
1972	5652	95.2
1973	6424	100.7
1974	5846	145.9
1975	5800	
1978 forecast		103.0
1979 forecast	7600	

---

2. Market Trends

Formaldehyde has had an annual growth rate of approximately 9.5 percent over the fifteen year period from 1960 to 1974 (Predicasts; 1975). Recent market slumps have been mainly due to the slowdown in the new home building industry, which uses large quantities of plyboard

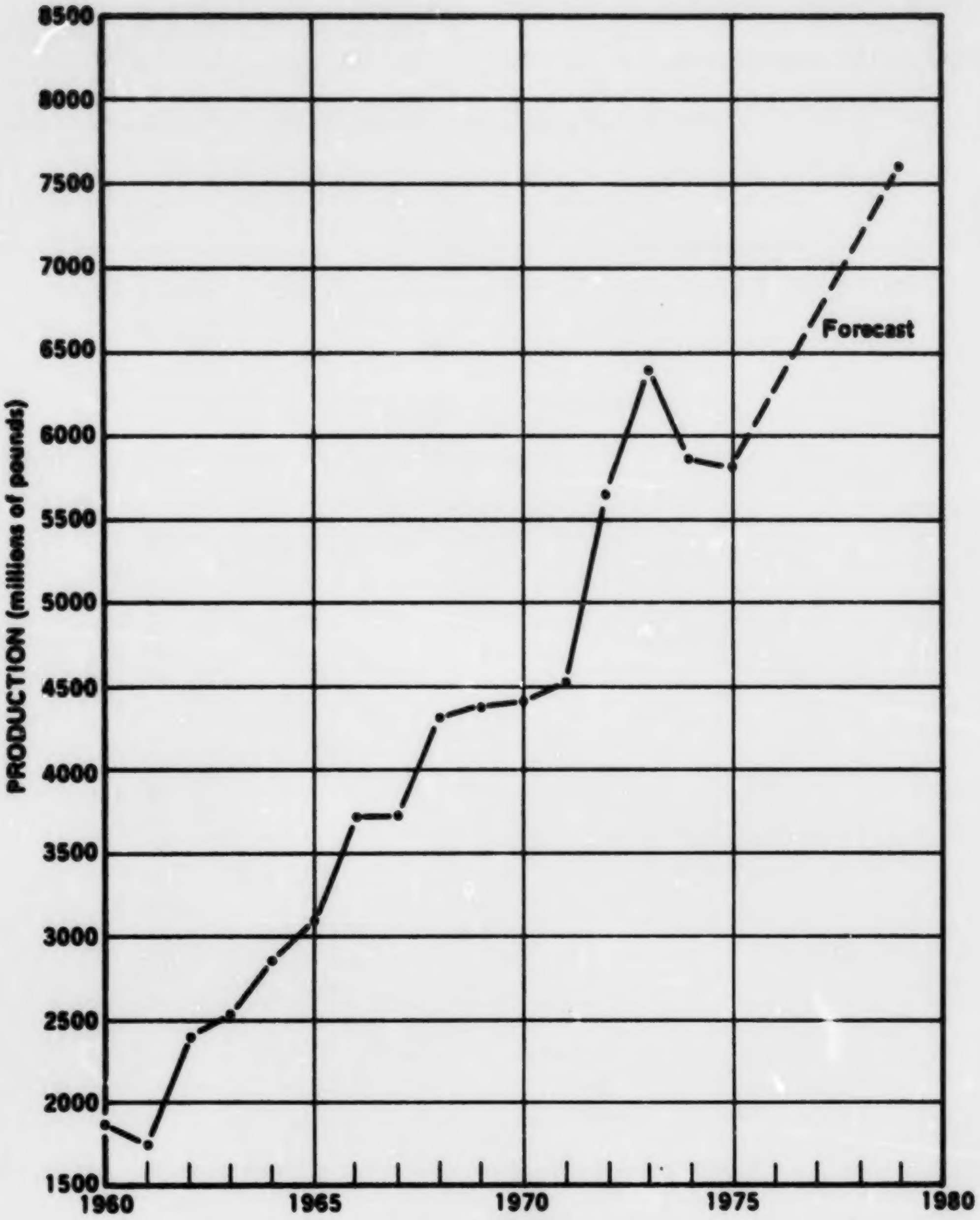


Figure 3. U. S. Formaldehyde Production
(U. S. Tariff Commission)

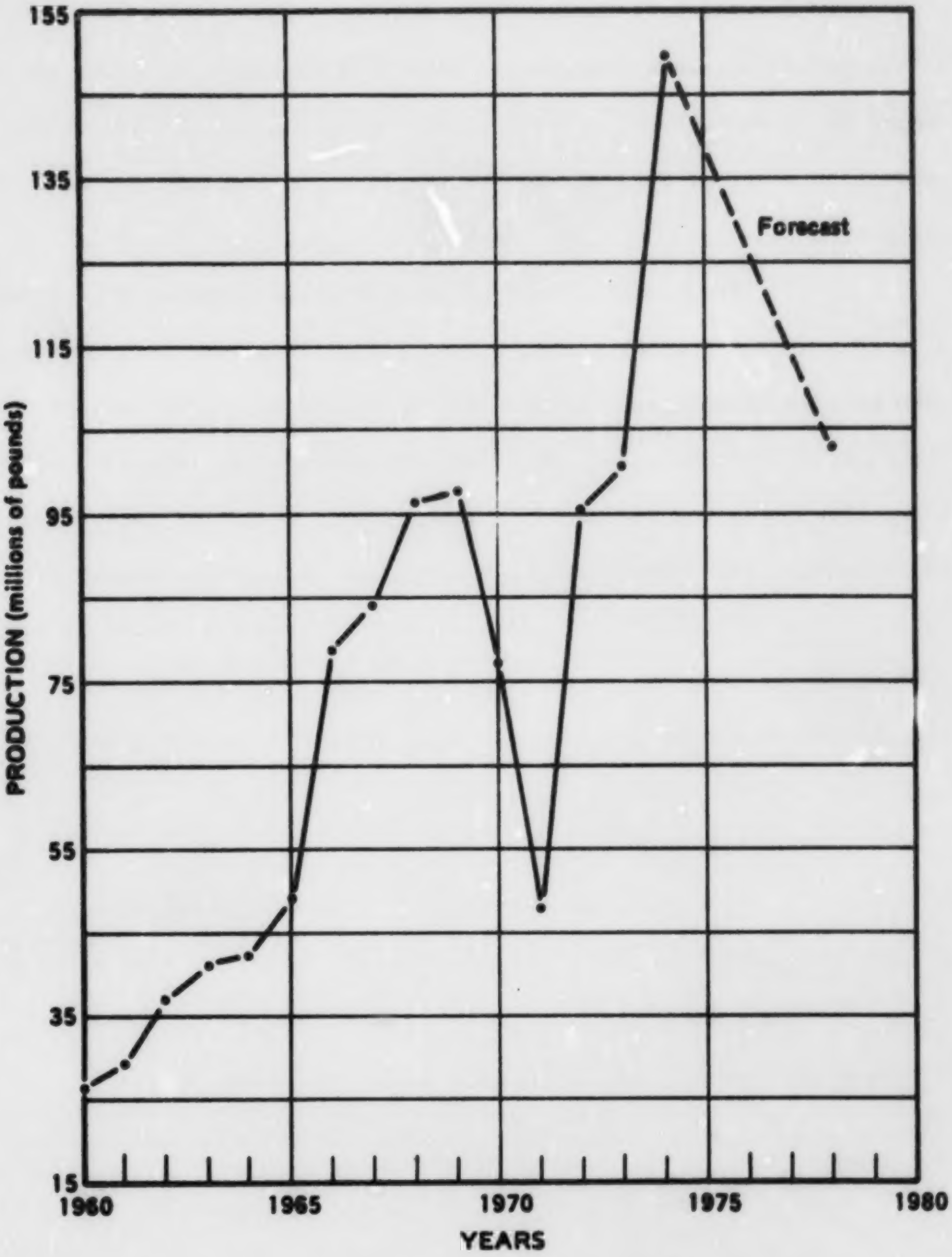


Figure 4. U. S. Hexamethylenetetramine Production
(U. S. Tariff Commission)

glued with formaldehyde resins. The housing industry is slowly recovering, as the nation's economy improves. With this recovery will come an increased demand for formaldehyde. Future predictions call for a total United States production level of 7600 million pounds by 1979 (Chemical Market Reporter, 1975).

Production levels of hexamethylenetetramine have grown at a rate of 9.4 percent annually over the fifteen year period from 1960 to 1974 (Predicasts, 1975). Future market forecasts call for declining production of hexamethylenetetramine. The predicted decline is mainly due to the reduction in manufacture of the military explosives RDX and HMX. Improvement in the housing and automobile industries will increase demands for phenolic resins. Hexamethylenetetramine is used as a crosslinking catalyst in these resins. Thus, the non-military uses of this compound will help offset the large military decline (Chemical Marketing Reporter, 1974).

3. Market Prices

The wholesale price of 37 percent uninhibited formalin in tank car quantities has fluctuated between a current high of $0.04 per pound to a low of $0.02 per pound. Historical price trends are listed in Table 11.

TABLE 11. Historical Price Trends for 37% Uninhibited Formaldehyde (U. S. Tariff Commission)

Year	1960-67	1968	1969	1970	1971	1972	1973	1974	1975
Price ($/lb)	0.03	0.02	0.02	0.02	0.02	0.02	0.02	0.03	0.04

Technical grade hexamethylenetetramine sold in bags in 20,000 pound lots has ranged in price from a low of $0.12 per pound to a current high of $0.32 per pound. Historical price trends are presented in Table 12.

TABLE 12. Historical Price Trends for Hexamethylenetetramine (U. S. Tariff Commission)

Year	Price ($/lb)	Year	Price($/lb)	Year	Price($/lb)
1960	0.21	1965	0.18	1970	0.15
1961	0.20	1966	0.18	1971	0.13
1962	0.19	1967	0.17	1972	0.12
1963	0.19	1968	0.15	1973	0.13
1964	0.18	1969	0.15	1974	0.22

4. Producers, Major Distributors, Importers, Sources of Imports and Production Sites

Formaldehyde is produced in the United States by seventeen different companies which maintain a total of 53 operational plants throughout the country. The formaldehyde and hexamethylenetetramine producers and the location of their facilities are listed in Table 13 and shown geographically in Figure 5. These facilities are concentrated in the Northeast, Pacific Northwest, Texas and the lumber producing areas of the South near formaldehyde consuming industries. The large number of plants and their locations are a result of two economic factors:

- captive production for product needs is less expensive than purchase.
- high expense associated with transport of aqueous solutions.

TABLE 13. Formaldehyde and Hexamethylenetetramine Producers and Facility Locations (Morris et al., 1973; Chemical Marketing Report, 1974, 1975; Personal Contacts)

Producer	Location	Formaldehyde Capacity (mil. lbs/year) Silver Catalyst Process	Formaldehyde Capacity (mil. lbs/year) Metal Oxide Process	Hexamethylenetetramine Capacity (mil. lbs/year)
Allied	Ironton, Ohio	300		
Borden	Demopolis, Alabama	80		
	Diboll, Texas	70		
	Fayetteville, North Carolina	200		24
	Fremont, California	80		
	Kent, Washington	70		
	La Grande, Oregon	40		
	Louisville, Kentucky	70		
	Missoula, Montana	80		
	Sheboygan, Wisconsin	120		
	Springfield, Oregon	260		
Celanese	Bishop, Texas	1300		
	Newark, New Jersey		117	
	Rock Hill, South Carolina		117	
Commercial Solvents	Sterlington, Louisiana	30		
	Seiple, Pennsylvania	80		
DuPont	Belle, West Virginia	485		
	Grasselli, New Jersey	150		
	Healing Spring, North Carolina	200		
	Strang, Texas	200		
	Toledo, Ohio	320		
GAF	Calvert City, Kentucky		100	
Georgia Pacific	Columbus, Ohio		100	
	Coos Bay, Oregon		80	
	Crossett, Arkansas	100	60	
	Albany, Oregon		100	
	Taylorsville, Mississippi		100	
	Vienna Georgia	100		
Gulf	Vicksburg, Mississippi		40	
Hercules	Louisiana, Missouri	170		
	Wilmington, North Carolina	95		
Hooker	N. Tonawanda, New York	135		28
Monsanto	Alvin, Texas	150		
	Addyston, Ohio	110		
	Eugene, Oregon	100		
	Springfield, Massachusetts	280		
Plastics Eng.	Sheboygan, Wisconsin			8
Reichhold	Hampton, South Carolina	36		
	Houston, Texas		100	
	Moncure, North Carolina		100	
	Tacoma, Washington		40	
	Tuscaloosa, Alabama	70		
	Kansas City, Kansas	40		
	White City, Oregon		50	
	Malvern, Arkansas		100	
Rohm and Haas	Philadelphia, Pennsylvania	25		
Skelly	Springfield, Oregon	70	70	
	Winfield, Louisiana		70	
Tenneco	Fords, New Jersey	105	160	22
	Garfield, New Jersey	105		
Union Carbide	Bound Brook, New Jersey		150	10
Wright	Acme, North Carolina		75	31
Dewey and Almy	Nashua, New Hampshire			Quantity Produced Not Available
	TOTAL	5,834	1,729	123

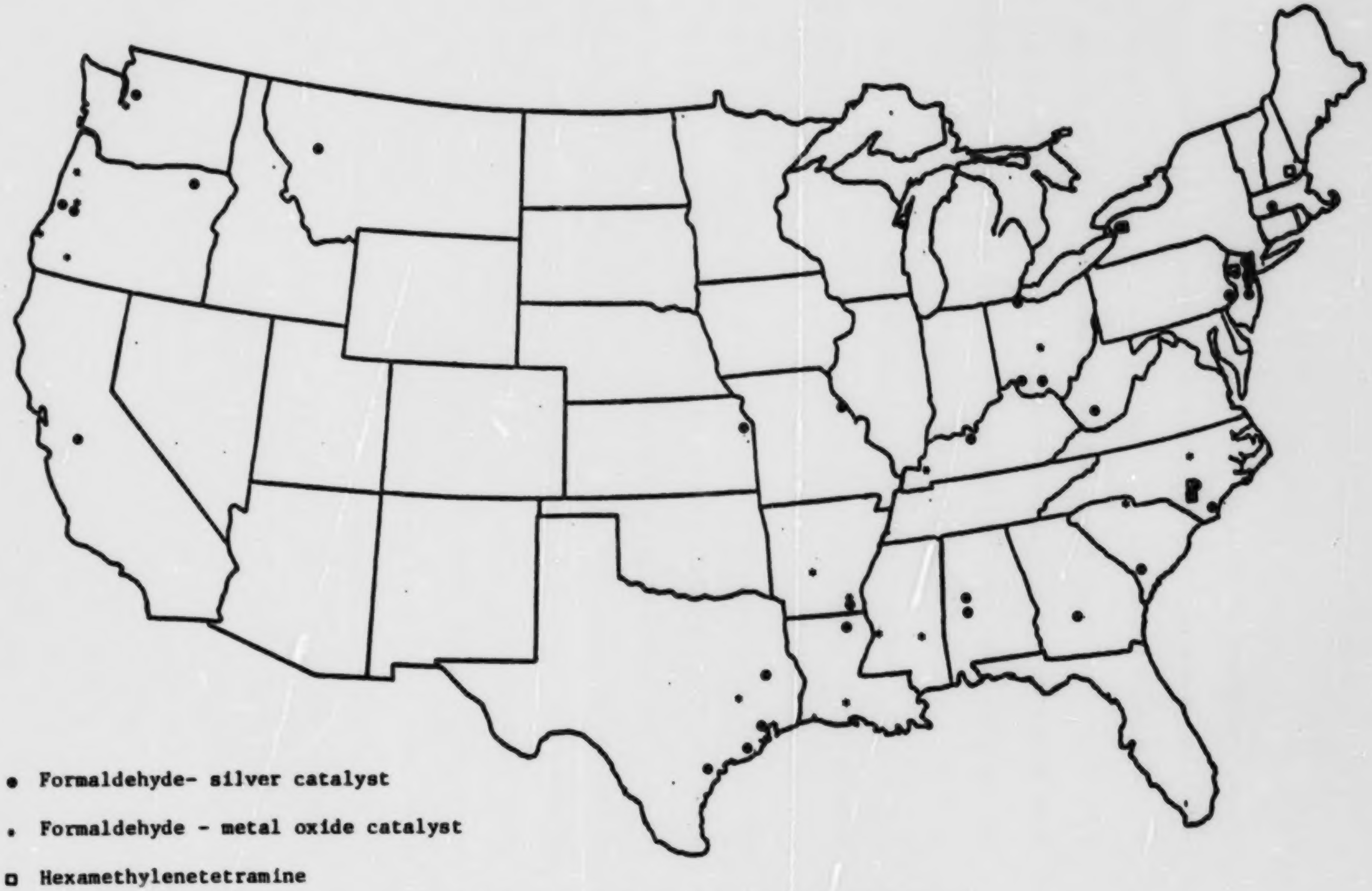

● Formaldehyde- silver catalyst
• Formaldehyde - metal oxide catalyst
□ Hexamethylenetetramine

Figure 5. Formaldehyde Production Sites

Captive production of formaldehyde is evidenced by the relatively small percentage of the total product which is sold commerically. Historically, this percentage ranged from a low of 30 percent in 1971 to a high of 46 percent in 1975. In contrast, hexamethylenetetramine sales typically represent 70 to 80 percent of the total product. In addition to the manufacturers, several other firms are distributors for formaldehyde and hexamethylenetetramine products. Major distributors are listed in Table 14.

Import figures for 37% formaldehyde, paraformaldehyde and hexamethylenetetramine are graphically displayed in Figure 6. Formaldehyde and hexamethylenetetramine were imported in large quantities in the sixties and early seventies, primarily from Canadian sources. Since the end of the Viet Nam conflict, imports of these chemicals have decreased drastically. Formaldehyde imports in 1972 and 1973 dropped to zero; hexamethylenetetramine to 9612 pounds in 1973. In contrast, paraformaldehyde imports in the 1970's have increased significantly. This increase in paraformaldehyde imports and the concurrent decrease in formalin are the result of rising shipping costs, making shipments of aqueous solutions impractical. Exports of formaldehyde comprise approximately two percent of the total product disposition (Chemical Marketing Reporter, 1975). No information was available as to the destination of the formaldehyde exports since the U. S. Tariff Commission figures are reported as total aldehyde and ketones.

TABLE 14. Major Distributors of Formaldehyde, Nascent Formaldehyde and Hexamethylenetetramine (Chemical Week, Oct. 1975)

	Formaldehyde	Hexamethylene-tetramine	Para-formaldehyde	Trioxane
Allied Chemical Co.	X			
American Firstoline	X			
Arenol Chemical Corp.	X			
Ashland Chemical Co.	X			
Borden Chemical	X	X		
Celanese Chemical	X		X	X
C & F Chemicals	X			
Chemical Dynamics Corp.	X			
Commercial Solvents	X			
Corco Chemical Corp.	X			
E. I. Dupont	X			
Durez Div., Hooker Chemical	X	X		
GAF Corp.	X			
Georgia Pacific	X			
Greeff and Company	X			
Hachik Bleach Co.	X			
Haven Chemical Co.	X			
Hercules, Inc.	X			
ICC Solvent Sales	X			
Intsel Chemical	X			
Jones Chemicals	X			
Mallinckrodt, Inc.	X			
Mann, George and Co., Inc.	X			
McKesson Chemical Co.	X	X	X	
Mitsubishi Gas Chemical	X	X		
Monsanto Chemical	X			
Narco Chemical	X			
Pacific Resins & Chemical	X			
Plastics Engineering Co.	X			
Reichhold Chemical	X			
Sobin Chemical	X			
Tenneco Chemical	X	X	X	
Thompson-Hayward Chemical	X		X	
Thorsen Chemical	X			
Ulte, George Co., Inc.	X			
Union Carbide Chemical	X			
Union Oil of California	X			
United Mineral and Chemical	X			
Van Waters and Rogers	X			
Wright Chemical	X	X		

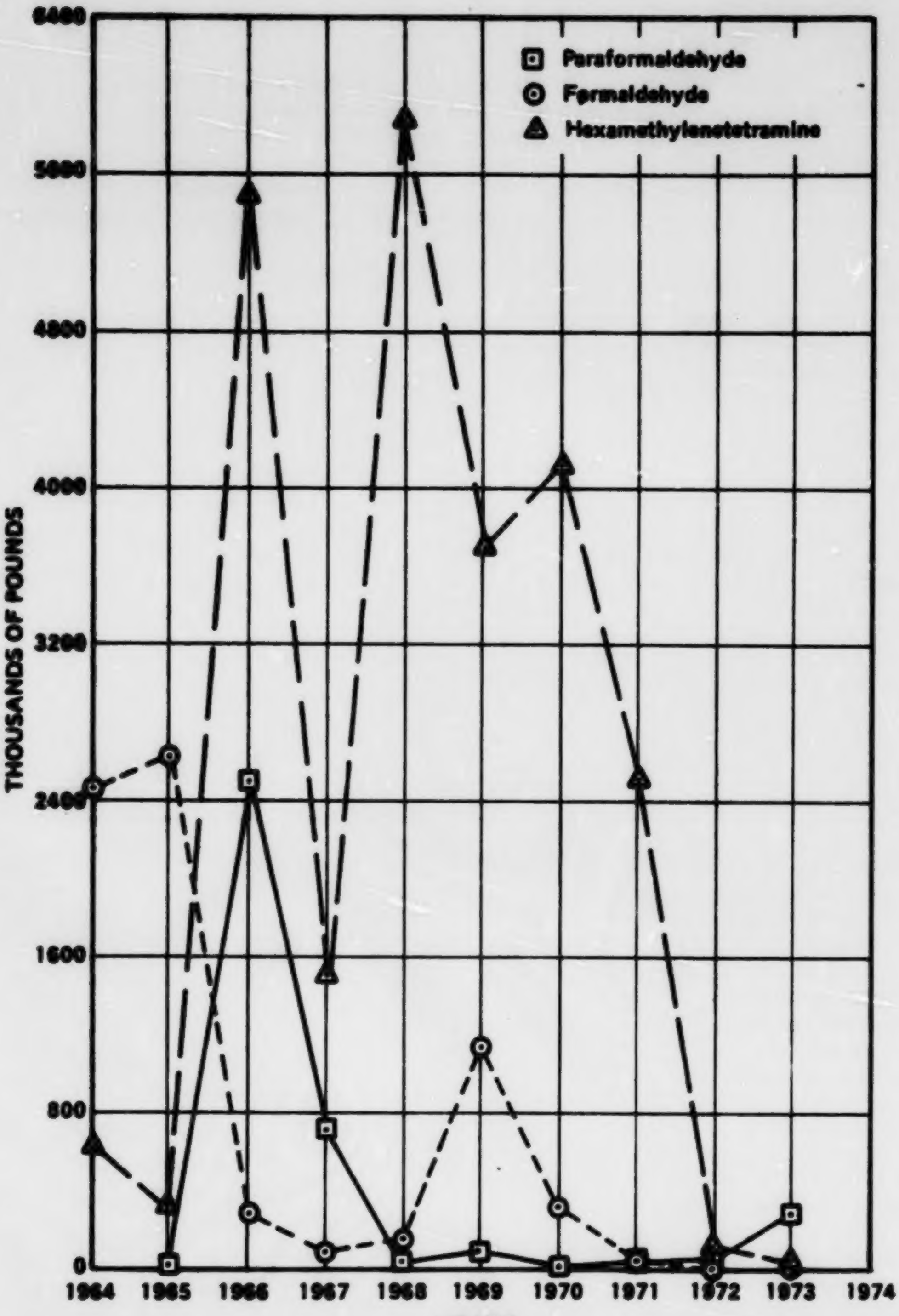


Figure 6. Imports of Formaldehyde, Paraformaldehyde and Hexamethylenetetramine (U. S. Tariff Commission)

5. Production Methods and Processes

a. Formaldehyde Production

Formaldehyde production in the United States is currently accomplished via two processes: the silver crystal catalyst process and the metal oxide catalyst process. Both production methods utilize methanol as the starting material. A third process was employed by Celanese in their Bishop, Texas, plant until its final shutdown in 1972 (Sawyer, 1976). This process was based upon the partial oxidation of light hydrocarbons to yield four major products: acetaldehyde, acetic acid, formaldehyde and methanol. The fluctuating markets for these products combined with the rising cost of hydrocarbon feed stock has reduced the economic competitiveness of the partial oxidation process.

Currently there are seventeen formaldehyde producers in the United States, operating plants in fifty-one locations. Total production capacity is estimated to be 7563 million pounds per year on a 37% basis. Of this total capacity, 77.1% is produced by the silver catalyst process and 22.9% by the metal oxide. The companies employing each of these processes, the plant locations, and capacity are listed in Table 13.

Silver Catalyst Process

Borden and ICI are the main licensers for the silver catalyst process in the United States. This process employs a methanol-rich air mixture which is passed over a stationary silver catalyst. Reaction conditions are approximately atmospheric pressure and temperatures of 450 to 650°C. The product gases are cooled and absorbed in water. Excess methanol is removed by distillation and returned to the process. Yields are typically 83 to 92% (Walker, 1966).

The formation of formaldehyde in the silver catalyst process is thought to involve the dyhydrogenation of methanol followed by combustion of the hydrogen product.

$$CH_3OH \rightleftharpoons CH_2O + H_2 \tag{5}$$

$$H_2 + 1/2O_2 \longrightarrow H_2O \tag{6}$$

Alternatively, a combination of dehydrogenation and oxidation has also been proposed:

$$CH_3OH \rightleftharpoons CH_2O + H_2 \tag{7}$$

$$CH_3OH + 1/2O_2 \longrightarrow CH_2O + H_2O \tag{8}$$

In addition to formaldehyde formation, other undesirable reactions can also occur if conditions permit. These reactions include pyrolysis of formaldehyde:

$$CH_2O \longrightarrow CO + H_2 \tag{9}$$

and further oxidation:

$$CH_2O + 1/2O_2 \longrightarrow HCOOH \longrightarrow CO + H_2O \tag{10}$$

or

$$CH_2O + O_2 \longrightarrow CO_2 + H_2O \tag{11}$$

The variations in the basic silver catalyst processes are the result of attempts to increase yield, decrease undesirable products formation, conserve energy and reduce pollutants. The history and the patent literature involved with process conditions selection is amply reviewed by Walker (1975) and will not be discussed here.

The flow sheets for the production of formaldehyde by the silver catalyst process are presented in Figures 7 and 8. Figure 7 is typical

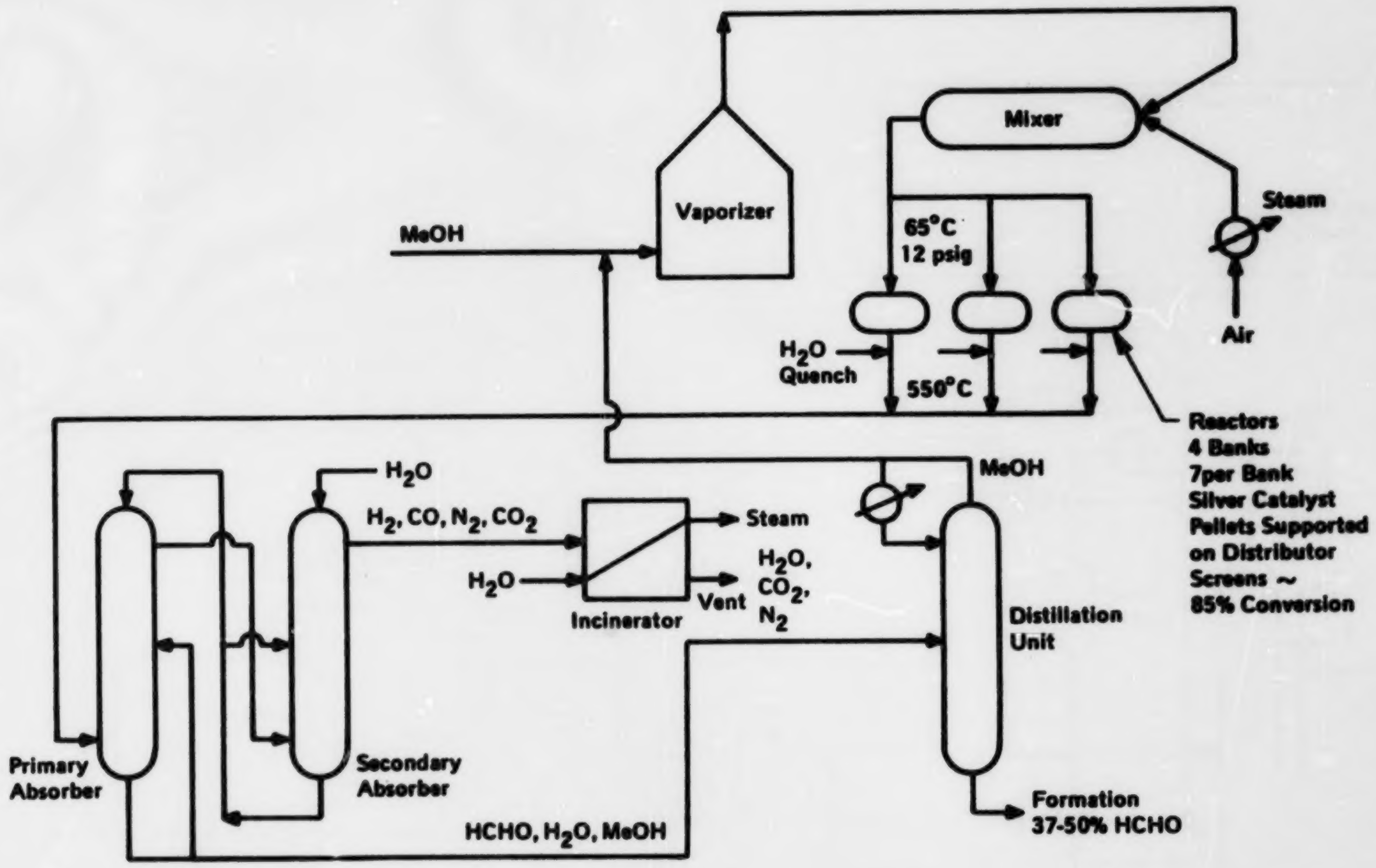

MeOH
Vaporizer
Mixer
Steam
Air
65°C
12 psig
H_2O
Quench
550°C
Reactors
4 Banks
7per Bank
Silver Catalyst
Pellets Supported
on Distributor
Screens ~
85% Conversion
H_2O
H_2, CO, N_2, CO_2
H_2O
Incinerator
Steam
Vent
H_2O, CO_2, N_2
MeOH
Distillation
Unit
Primary
Absorber
Secondary
Absorber
HCHO, H_2O, MeOH
Formation
37-50% HCHO

Figure 7. Formaldehyde Production
Borden Silver Catalyst Process

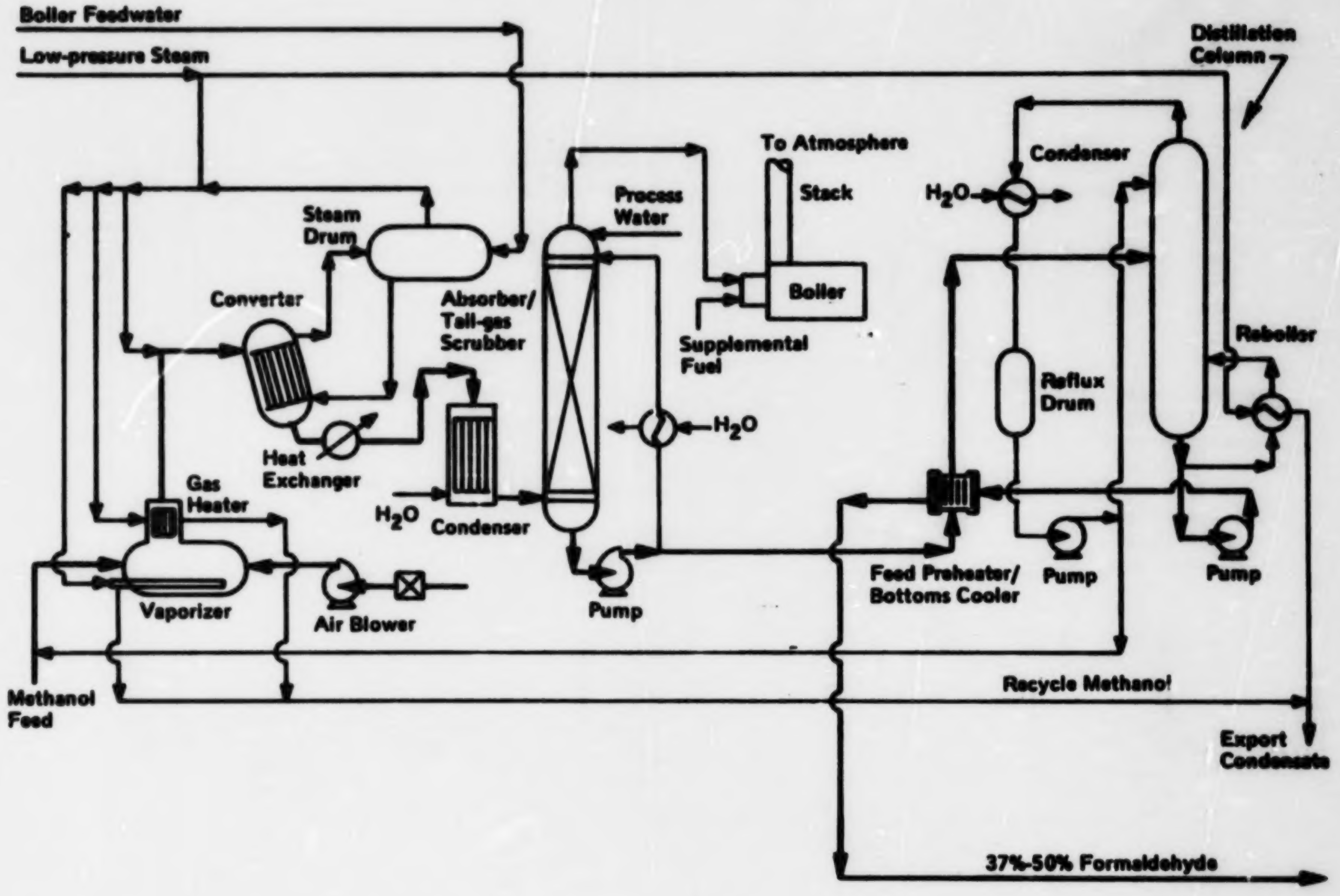

Boiler Feedwater
Low-pressure Steam
Distillation Column
To Atmosphere
Stack
Condenser
H_2O
Steam Drum
Process Water
Boiler
Converter
Absorber/ Tail-gas Scrubber
Supplemental Fuel
Reboiler
Reflux Drum
H_2O
Heat Exchanger
Gas Heater
H_2O
Condenser
Feed Preheater/ Bottoms Cooler
Pump
Pump
Pump
Vaporizer
Air Blower
Methanol Feed
Recycle Methanol
Export Condensate
37%-50% Formaldehyde

Figure 8. Formaldehyde Production - ICI Silver Catalyst Process (Martin and Butler, 1974) Reprinted with Permission

of the Borden process; Figure 8 of the ICI process. The similarities and differences are discussed in the following process description.

(1) The initial step in both production methods is the removal of CO_2 and sulfur compounds from the process air by a caustic wash.

(2) As normally employed in the Borden process, fresh methanol from storage and recycle methanol are superheated to ∿57°C and 12 psig. The superheated methanol is then mixed with the air in a mole ratio of oxygen/methanol of about 1:4. In the ICI process (Figure 8), a constant amount of steam is added to the air/methanol mixture, usually after heating and mixing has taken place. However, some plants mix water directly with liquid methanol and flash the mixture. The presence of water vapor is reported to lower the reaction temperature, increase formaldehyde yield, and decrease undesirable reactions (Thomas, 1920).

(3) The heated mixture is then passed through the silver catalyst reactor(s) where conversion to formaldehyde occurs. The Borden process employs a large number of reactors, whereas the ICI design utilizes only one reactor. The number and size of the reactors is dependent upon the manner in which the catalyst is supported and the ability to control the temperatures. High temperatures are the result of heat generated by the exothermic oxidation reaction. These temperatures must be maintained below 650°C in order to prevent pyrolysis or further oxidation.

(4) Once past the catalyst bed, the hot gases must be quenched to

prevent decomposition. In the Borden process, this quenching is accomplished by an absorber system which is closely coupled to the reactors. The primary absorber is usually a Raschig ring packed tower. The absorber liquid is an aqueous formaldehyde/methanol mixture containing 20 to 22% formaldehyde and 28 to 30% methanol (Morris _et al._, 1975a). The product liquid from the primary absorber is sent to distillation columns. The gases are blown to a second absorber column where distilled water is used as a scrubbing solution. The dilute formaldehyde/methanol bottoms from this column are used as the absorber liquid in the primary column. The gases from the secondary absorber have normally been vented to the atmosphere in the past. These absorber tail gases contain CO and 18 to 20% H_2 (Walker, 1966). The fuel value of these gases is being reclaimed in many plants by incineration to generate steam. This modification significantly reduces pollution and also results in energy savings.

ICI utilizes a different system to quench the hot gases from the reactor. In this process, the hot gas (∿600°C) from the reactor is immediately passed through a heat exchanger to lower the temperature to 150°C. The heat from the exchanger is used to produce steam at 30 psig (Martin and Butler, 1974). After leaving the exchanger, the gases are passed into a water-cooled condenser where most of the formaldehyde/methanol gases are liquified. The liquid and the uncondensable gases, such as H_2, CO, N_2, CO_2 are passed to the lower section of an absorber. The final scrubbing of the gases is accomplished at the top of the absorber column using water as the absorber liquid. The absorber tail gases are passed to a boiler for incineration to control pollution and conserve energy.

(5) The methanol content of the product from the absorbers must be adjusted to fit the current demand. This is accomplished by fractionation in a vacuum column. Methanol, the overhead product in this process, is recirculated to the vaporizer. The bottoms product is 37 to 50% formalin having a methanol content of less than 1%, if desired.

(6) If necessary, formic acid is removed by ion exchange in the last step of the process.

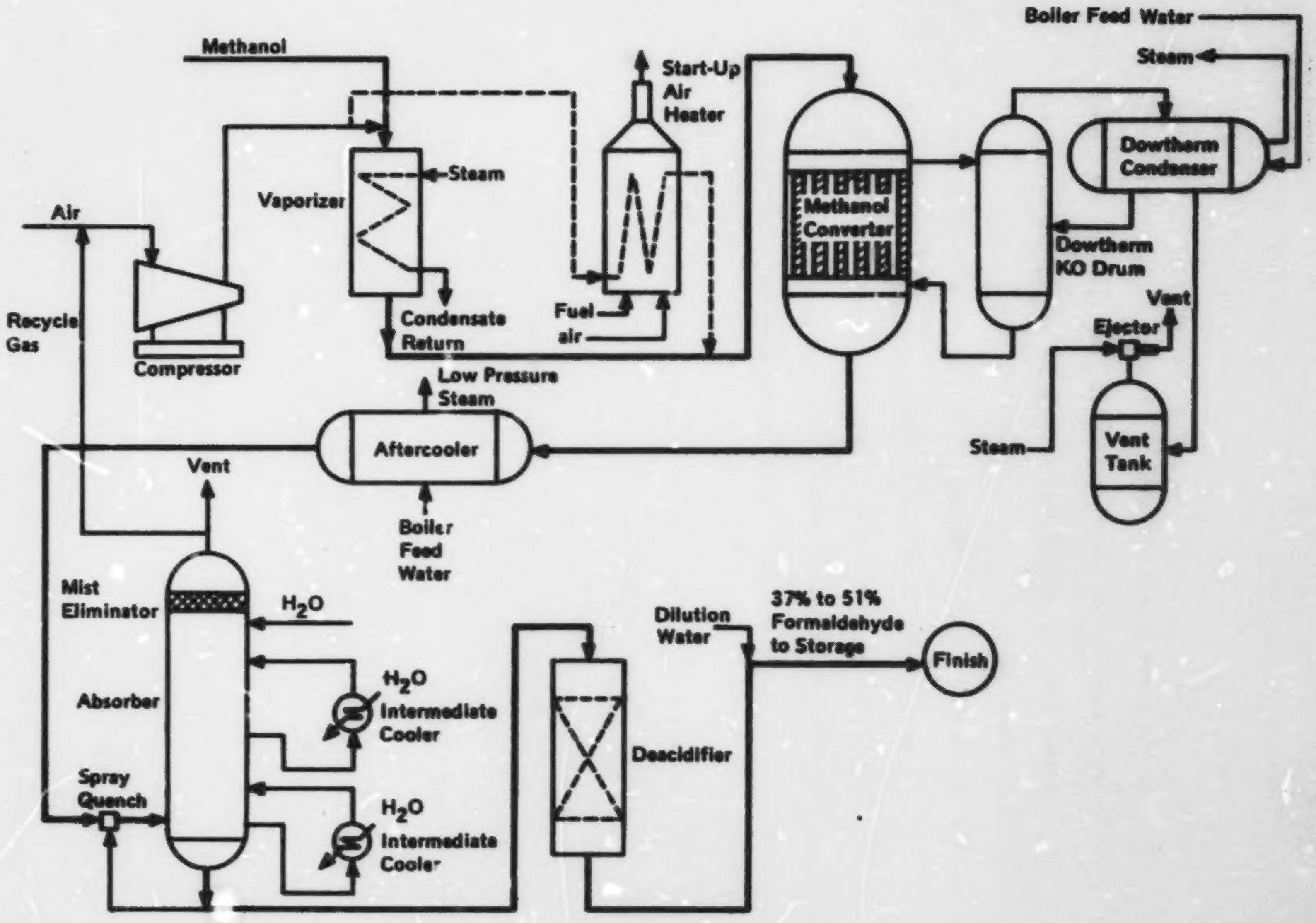
Metal Oxide Catalyst Process

The metal oxide catalyst process is licensed in the United States by Reichhold and Lummus. This process converts methanol to formaldehyde by oxidation:

$$CH_3OH + 1/2O_2 \longrightarrow CH_2O + H_2O \qquad (12)$$

The catalysts employed in this selective oxidation process are usually iron-molybdenum oxide mixtures. The reactant mixture is air rich, containing only 5 to 10 volume percent methanol (Morris et al., 1975b). The formaldehyde formed is low in methanol content, usually less than one percent. The yield for the metal oxide process is reported to be higher than that for the silver catalyst.

A typical flow sheet of the metal oxide catalyst process is presented in Figure 9 and described below.



Methanol
Start-Up
Air
Heater
Boiler Feed Water
Steam
Dowtherm
Condenser
Steam
Vaporizer
Air
Methanol
Converter
Dowtherm
KO Drum
Vent
Ejector
Recycle
Gas
Compressor
Condensate
Return
Fuel
air
Low Pressure
Steam
Aftercooler
Steam
Vent
Tank
Vent
Boiler
Feed
Water
Mist
Eliminator
H_2O
Dilution
Water
37% to 51%
Formaldehyde
to Storage
Finish
H_2O
Intermediate
Cooler
Absorber
Deacidifier
Spray
Quench
H_2O
Intermediate
Cooler

Figure 9. Formaldehyde Production - Metal Oxide Process (Morris et al., 1975b)

(1) Methanol and air/recycle gas are combined and heated in a steam-jacketed vaporizer to between 105 and 177°C. This feed stream usually contains about 9.5 volume percent methanol and 10 volume percent oxygen (Morris et al., 1975b).

(2) Once heated to the correct temperature, the gaseous mixture is passed into the converter. The converter consists of a series of tubes filled with the metal oxide catalyst. Temperatures in the reaction zone range from 340 to 425°C. Reaction control is maintained by removal of excess heat by means of a heat exchanger fluid circulating around the catalyst tubes. The heat from the exchanger fluid is used to produce steam.

(3) The hot gases (260°C) from the converter are passed through a water-cooled heat exchanger to lower their temperature to 105°C.

(4) From the heat exchanger, the gases pass into the bottom of a bubble cap absorber column having a water flow counter-current to the gas flow. The aqueous formaldehyde solution exits through the bottom and the noncondensables through the top of the column.

b. Paraformaldehyde

Paraformaldehyde is normally produced from formalin solutions. These solutions are vacuum distilled until polymer precipitation occurs. The distillation process conditions are controlled so that the final product has the desired formaldehyde content and solubility properties. Commercial paraformaldehyde is available in formaldehyde content ranging from 91 to 99%. The water solubility properties are controlled by the pH during the precipitation. pH ranges <1.0 and >6.5 favor a highly soluble product, while pH between 1.0 and 6.5 leads to insoluble paraformaldehyde. The distillate vapors are condensed yielding a dilute formaldehyde solution. The polymer resulting from the process is dried, flaked and packaged.

c. Trioxane

Trioxane is prepared from formalin solution by distillation in the presence of either sulfuric acid or acidic ion-exchange resin containing $-SO_3H$ groups. The distillate is an azeotrope of trioxane, formaldehyde and water boiling at ∿90°C. The trioxane is separated from the distillate by extraction with a water immiscible material, such as methylene chloride (Walker and Carlisle, 1943), or α-chloronaphthalene. The trioxane is recovered by distillation or crystallization.

d. Hexamethylenetetramine

Hexamethylenetetramine is prepared by the addition of gaseous or aqueous ammonia in the proper stoichiometric quantities to formalin solutions. The reaction proceeds almost quantitatively according to the following equation:

$$6CH_2O + 4NH_3 \longrightarrow C_6H_4N_4 + 6H_2O \qquad (13)$$

The flow sheet for the manufacture of hexamethylenetetramine is presented in Figure 10 and described below.

(1) The reactor feed consists of ammonia gas and a 37% uninhibited formalin solution.

(2) In the reactor, this mixture is controlled to a pH of 7 to 8 and a temperature between 30 and 50 °C to prevent decomposition of the product. Temperature control is maintained by a water cooled heat exchanger. Conversion takes 4 to 5 hours.

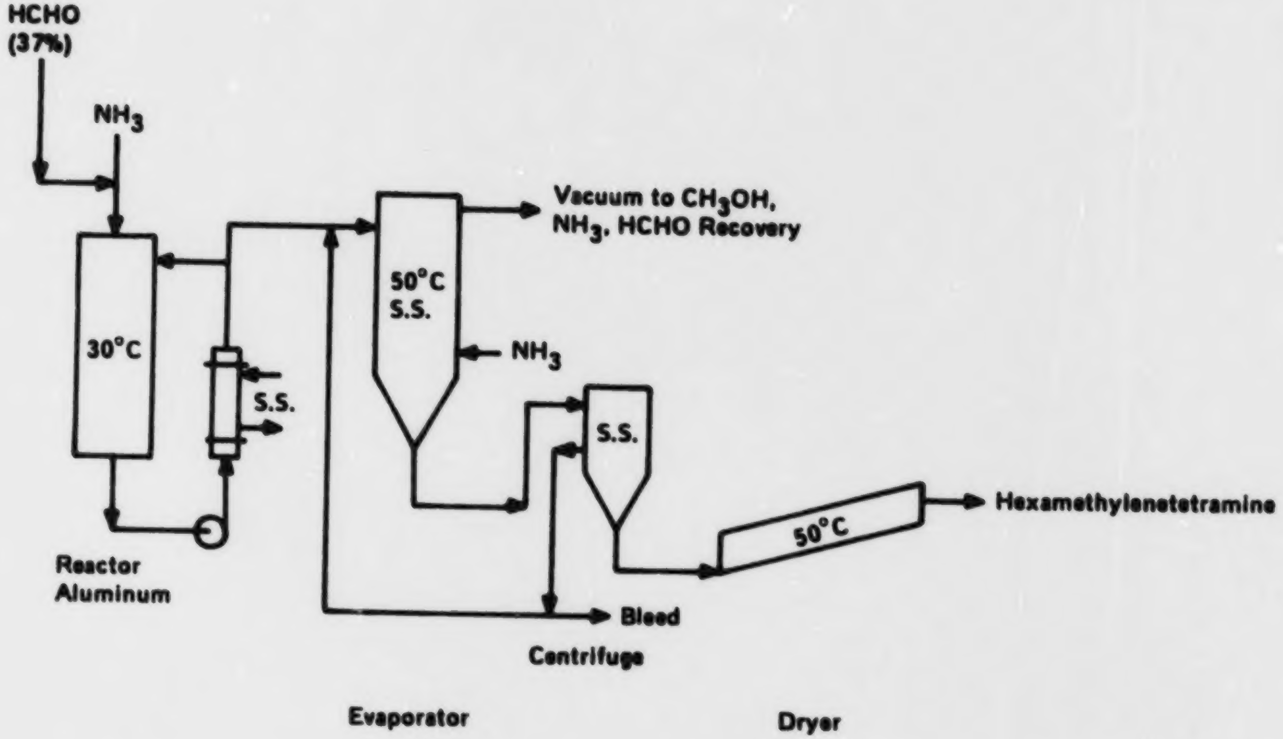

HCHO (37%)
NH_3
30°C
Reactor Aluminum
S.S.
50°C S.S.
Vacuum to CH_3OH, NH_3, HCHO Recovery
NH_3
S.S.
Bleed
Centrifuge
Evaporator
50°C
Dryer
Hexamethylenetetramine

Figure 10. Manufacture of Hexamethylenetetramine
(Sherwood, 1958)
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(3) The reactor effluent is passed into a vacuum evaporator where the product is concentrated and excess reactants removed. Addition of ammonia in this step helps to prevent decomposition of the hexamethylenetetramine. Temperatures are maintained at ∿50°C to aid in precipitation.

(4) The slurry from the evaporator is centrifuged, washed, and sent to the drier. Drier temperatures are also maintained at 50°C or below.

B. USES

1. Major Uses

Formaldehyde is one of the most widely used industrial chemicals. Its utility is due to many factors, including high reactivity, low cost, availability, purity of commercial forms, and its colorless nature. The current major uses of formaldehyde are listed in Table 15, along with the percentage of the total formaldehyde product devoted to each use.

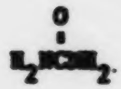
TABLE 15. Major Uses of Formaldehyde (Chemical Marketing Reporter, 1975)

Use	Percentage of Formaldehyde Product
Urea-formaldehyde resins	25
Phenolic resins	21
Polyacetal resins	8
Pentaerythritol	7
Hexamethylenetetremine	5
Melamine-formaldehyde resins	3
Exports	2
Other	29

Inspection of Table 15 reveals that over 50% of the formaldehyde produced is used in the manufacture of resins. These resins find a variety of uses in modern day society. Their importance and their potential for releasing formaldehyde into the environment warrants their further discussion.

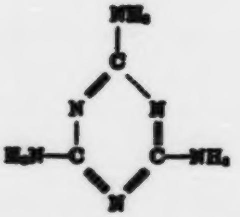
a. Amino-Formaldehyde Resins

The amino-formaldehyde resins manufactured in large quantities are those produced by the condensation of urea



$H_2N\overset{\overset{O}{\|}}{C}NH_2$.

or melamine



with formaldehyde. The initial step in the synthesis is the formation of a methylol derivative by condensation of formaldehyde with a reactive amino or amide hydrogen:

$$R\text{-}NH_2 + CH_2O \rightleftharpoons R\text{-}NH\text{-}CH_2OH \qquad (14)$$

These methylol derivatives are highly reactive and can undergo a variety of reactions yielding resins with specific physical and chemical properties. Under acidic conditions further condensation can occur with the formation of methylene bridges:

$$R'NH_2 + HOCH_2\text{-}NH\text{-}R \longrightarrow R'NH\text{-}CH_2\text{-}NH\text{-}R + H_2O \qquad (15)$$

Ether formation can also occur if the pH, time and temperature are in the proper range and the formaldehyde/amino ratio is high.

$$R\text{-}NH\text{-}CH_2OH + HOCH_2\text{-}NH\text{-}R \longrightarrow R\text{-}NH\text{-}CH_2O\text{-}CH_2\text{-}HN\text{-}R \qquad (16)$$

Ether formation is undesirable in molding powders or laminating resins, due to the instability of the ether in the high temperature and conditions used in the molding process. Under these conditions the ether breaks to form formaldehyde and a methylene bridge, resulting in shrinking and cracking of the plastic curing molding.

The methylol derivatives can also undergo alkylations:

$$R\text{-}NH\text{-}CH_2OH + HOR' \longrightarrow R\text{-}NH\text{-}CH_2\text{-}OR' + H_2O \qquad (17)$$

This process is used in the preparation of organic solvent-soluble resins for surface coatings. The alkylated derivatives can undergo alcohol displacement:

$$R\text{-}NH\text{-}CH_2O\text{-}R' + HOR'' \longrightarrow R\text{-}NH\text{-}CH_2O\text{-}R'' + HOR' \qquad (18)$$

Curing of amino resin modified alkyd baking enamel utilizes this type of displacement.

The major producers of urea-formaldehyde and melamine-formaldehyde resins in the United States are listed in Table 16.

TABLE 16. Urea- and Melamine-Formaldehyde Resins Producers (U. S. Tariff Commission)

Producer	Urea	Melamine	Producer	Urea	Melamine
Allied Chemical Corp.	X	X	E. I. Dupont de Nemours & Co.	X	X
American Cyanamid	X	X	Exxon		X
Ashland Oil, Inc.	X		Formica Corp.		X
Borden Co.	X	X	GAF Corp	X	
Carborundum Corp.	X		Georgia Pacific Corp.	X	
Cargill, Inc.	X	X	Guardsman Chemical Coating	X	X
Celanese Corp.	X	X	Gulf Oil Corp.	X	
Chembond Corp.	X	X	Hanna Chemical Coating	X	X
Conchemco, Inc.	X	X	H & N Chemical Co.	X	
Cook Paint & Varnish Co.	X	X	Hercules Inc.	X	
Crown Metro, Inc.	X	X	Hart Products Corp.	X	
Dan River, Inc.	X	X	Inmont Corp.		X
De Soto, Inc.		X	Jersey State Chemical Co.	X	X
E.F. Houghton & Co.	X		Koppers Co.	X	X

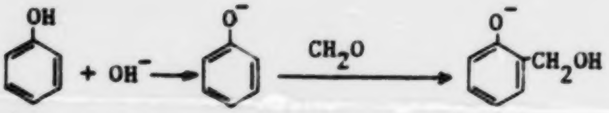
Producer	Urea	Melamine
Millmaster Onyx Corp.	X	X
Minnesota Mining	X	
Mobile Oil Corp.	X	X
Monsanto Corp.	X	X
National Casein Co.	X	
Pacific Resin & Chemical	X	X
Pioneer Plastics Corp.	X	X
Pittsburgh Plate Glass	X	X
Proctor Chemical Co.	X	
Quaker Chemical Corp.		X
Reichhold Chemicals	X	X
Reliance Universal Inc.	X	X
Rohm and Haas Co.	X	X
SCM Corp.	X	
Scher Bros, Inc.		X
Sherwin-Williams Co.	X	X
Son-Tex Chemical Co.		X
Southwester Adhesive	X	
Storey Chemical Corp.	X	
Sun Chemical Corp.	X	X
Thomason Industries	X	
Textilana Corp.	X	
United-Erie, Inc.	X	
U. S. Oil Co.	X	
U. S. Plywood	X	
Valchem	X	X
Weyerhauser Co.	X	X
Wright Chemical Co.	X	

The major markets for these resins and their consumption over the last five years is presented in Table 17.

b. Phenolic Resins

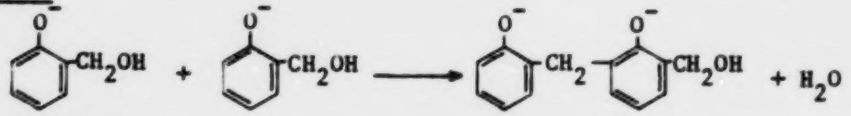
Phenols, having at least one opening in the 2,4 or 6 ring positions, react with formaldehyde to form resins by an addition condensation process. This process is catalyzed by both acids and bases. The base catalyzed reactions proceed as follows:

addition



(19)

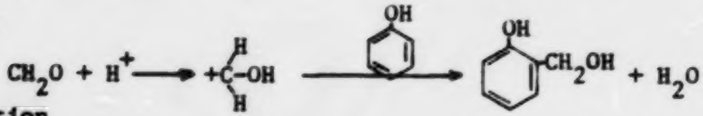
condensation



(20)

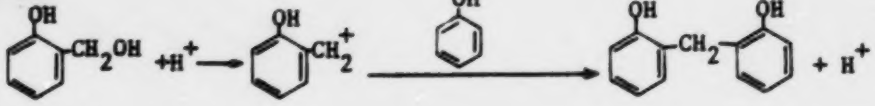
Under acid conditions, the following reactions occur:

addition



(21)

condensation



(22)

TABLE 17. Urea- and Melamine-Formaldehyde Resins Markets (Modern Plastics, 1972; 1973; 1974a; 1975; 1976)

Market	Use by Year in 1000 tons				
	1971	1972	1973	1974	1975
Bonding and adhesive resins for:					
1. Fibrous & granulated wood	199.0	232.0	278.5	264.0	171.6
2. Laminating	22.0	24.0	26.2	21.0	13.7
3. Plywood	31.0	40.0	40.1	43.0	28.0
Molding Compounds					
1. Urea					
a. Closures	6.9	6.8	7.6	7.1	5.6
b. Electrical devices	11.4	10.9	12.5	12.7	10.9
c. Other	2.7	2.3	2.2	2.0	1.6
2. Melamine					
a. Buttons	0.9	0.8	0.8	0.6	1.2
b. Dinnerware	19.1	18.2	19.0	18.3	15.8
c. Sanitary ware	-	0.5	0.5	0.3	0.3
d. Other	0.9	0.5	0.4	0.3	0.3
Paper treating & coating resins	14.0	16.0	24.0	25.0	15.9
Protective coatings	19.0	28.0	35.2	37.0	19.1
Textile treating & coating resins	23.0	23.0	27.0	28.0	18.2
Exports	4.0	5.0	11.1	13.0	4.2
Other	3.0	3.0	3.0	2.2	2.0
TOTAL	357.0	411.0	488.1	474.5	308.4

The type of resin formed is controlled by the amount of ring substitution, the phenol/formaldehyde ratio and the catalyst.

The novolaks are fusible resins formed by linear condensation of monomethylol phenol. This thermosetting resin is a fusible, brittle solid which can be dissolved in a variety of organic solvents. It will melt upon heating, but will not undergo cross linking. The novolaks are formed with an acid catalyst and a formaldehyde/phenol ratio of less than one. Under these conditions, the monomethylol phenol is condensed as rapidly as it is formed.

For most uses, the novolaks are subjected to a second step. In this step, they are fused with hexamethylenetetramine in the presence of an alkaline catalyst. This process cross-links and hardens the resin to make a thermosetting molding powder.

The resols are infusible resins of a highly cross-linked structure. They are produced from phenols in which the 2, 4, and 6 ring positions are unsubstituted in a single-step process utilizing a base catalyst. The mole ratio of formaldehyde/phenol employed is greater than one.

The major manufacturers of phenolic resins are listed in Table 18. Table 19 lists the major uses for these resins and the market trends for the past five years.

c. Polyacetal Resins

The polyacetal resins can be divided into two groups: the homopolymers and the copolymers. The homopolymers are high molecular weight polyoxymethylene. The end groups are usually modified to prevent

TABLE 18. Phenolic Resins and Molding Compound Producers (Modern Plastics, 1974b)

Producer	Current Capacity 1000 metric tons	Estimated Capacity mid-1975, 1000 metric tons
Phenolic Resins:		
Ashland	30	30
Borden	20	20
Durez	140	150
Monsanto	50	55
Plenco	35	50
Reichhold	165	180
Union Carbide	90	90
Others	195	225
TOTAL	725	800
Phenolic Molding Compounds:		
Durez	68.2	
Plenco	27.3	
Union Carbide	22.7	
Reichhold Chemicls	15.9	
Fiberite	6.8	
Valite	4.5	
Rogers	2.3	
Others	35.4	
TOTAL	183.1	

TABLE 19. Phenolic Resins Markets (Modern Plastics, 1972; 1973; 1974a; 1975; 1976)

	Use by Year in 1000 m Tons				
Market	1971	1972	1973	1974	1975
Bonding and adhesive resin for					
1. Coated and bonded abrasives	8.0	9.1	11.2	13.5	10.2
2. Fibrous & granulated wood	30.0	40.0	42.0	25.9	10.8
3. Friction materials	14.0	13.4	14.7	14.8	10.6
4. Foundry & shell moldings	39.0	43.6	50.0	36.5	24.5
5. Insulation materials	88.0	107.0	112.0	103.5	74.5
Laminating					
1. Building	21.5	26.1	26.2	23.0	15.0
2. Electrical/electronics	7.0	7.3	7.3	6.7	6.0
3. Furniture	12.0	16.0	17.0	15.0	10.0
4. Other	2.5	2.7	2.7	2.1	1.7
Plywood	152.0	163.3	125.0	136.8	124.0
Molding Compounds					
1. Appliances	17.5	31.8	41.4	35.0	20.0
2. Business Machines	4.4	6.1	6.8	5.5	3.5
3. Closures	9.1	4.5	4.1	3.5	3.0
4. Electrical/electronics					
a. Controls & switches	40.4	56.0	61.0	56.0	30.0
b. Telephone & communications	9.8	9.3	9.5	8.0	5.0
c. Wiring	15.6	15.9	16.3	16.5	10.0
5. Housewares					
a. Utensils & handles	11.2	14.3	14.7	13.5	11.0
b. Other	3.5	4.7	5.3	4.0	2.5
6. Machine parts, etc.	4.0	4.8	5.1	4.5	3.0
7. Other	1.5	8.2	8.9	3.5	2.0
Protective Coatings	10.0	9.6	10.1	10.0	5.9
Exports	9.0	13.1	13.6	11.2	6.8
Other	30.0	44.0	48.6	41.0	24.0
TOTAL	540.0	650.8	653.5	590.0	414.0

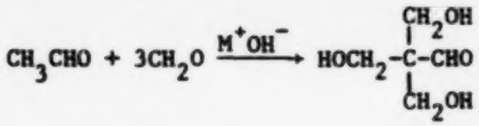
decomposition. This process, known as end-capping, is accomplished by chemical replacement of the glycol by other more stable groups such as acyl or alkyl (Walker, 1975). The homopolymers possess high strength and rigidity, as well as good frictional properties, high melt point and resistance to fatigue. E. I. Dupont is the major manufacturer of the homopolymers. They are marketed under the name of DELRIN®.

Acetal copolymers are manufactured by Celanese Plastics Company under the trade name CELCON®. These highly-crystalline thermoplastics are prepared by copolymerization of trioxane with small amounts of comonomer. This comonomer randomly distributes C-C bonds in the polymer chain. The resulting C-C bonds help stabilize the acetal copolymers against thermal, oxidative and acid attack (Serle, 1975).

Polyacetal resins are used for a variety of purposes, as illustrated in Table 20.

d. Pentaerythritol

Pentaerythritol is prepared from formaldehyde and acetaldehyde in the presence of an alkali metal or alkaline earth hydroxide. The reaction involves the aldol condensation of three molecules of formaldehyde with one molecule of acetaldehyde to form pentaerythrose

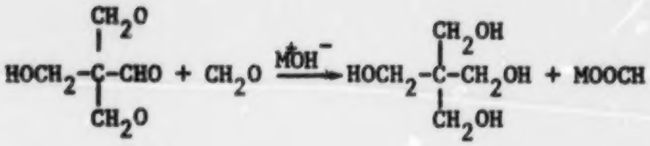


$$CH_3CHO + 3CH_2O \xrightarrow{M^+OH^-} HOCH_2-\underset{CH_2OH}{\overset{CH_2OH}{\overset{|}{\underset{|}{C}}}}-CHO \qquad (23)$$

This reaction is followed by a crossed Cannizzaro reaction between pentaerythrose and formaldehyde resulting in the formation of pentaerythritol.

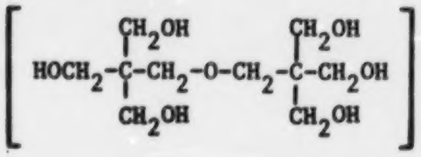
TABLE 20. Polyacetal Resins Markets
(Modern Plastics, 1972; 1973;
1974a; 1975; 1976)

Market	Use by Year in 1000 m Tons				
	1971	1972	1973	1974	1975
Appliances	4.82	5.46	5.9	5.6	4.9
Consumer Products	3.09	3.45	3.8	3.7	3.6
Electrical/Electronics	1.91	2.14	2.5	2.3	1.8
Machinery Parts	2.55	2.82	3.9	4.1	4.0
Plumbing and Hardware	2.55	2.82	4.0	3.8	3.3
Sheet, Rod, Tube	1.32	1.46	1.8	1.7	1.7
Transportation	6.05	6.73	6.5	5.6	4.0
Other	2.27	2.50	3.0	2.9	2.5
TOTAL	24.56	27.38	31.4	29.7	25.8



$$\mathrm{HOCH_2-\underset{CH_2O}{\overset{CH_2O}{C}}-CHO + CH_2O \xrightarrow{\overset{+}{M}OH^-} HOCH_2-\underset{CH_2OH}{\overset{CH_2OH}{C}}-CH_2OH + MOOCH} \qquad (24)$$

Some dipentaerythritol is also formed in the reaction.



$$\left[\mathrm{HOCH_2-\underset{CH_2OH}{\overset{CH_2OH}{C}}-CH_2-O-CH_2-\underset{CH_2OH}{\overset{CH_2OH}{C}}-CH_2OH}\right]$$

Pentaerythritol finds its main uses in alkyd surface coating resins, rosin and tall oil resins, varnishes, pharmaceuticals, plasticizers and insecticides (Dupont, 1976). These resins are superior to the gylcerols in drying speed, hardness, gloss, flexibility and durability. During wartime production, pentaerythritol tetranitrate, PETN, was a major pentaerythritol user. This explosive is prepared by nitration of pentaerythritol with a mixture of nitric and sulfuric acids. However, at present PETN only uses ∿ 3.5% of the pentaerythritol produced. Producers and production figures for pentaerythritol are given in Tables 21 and 22.

TABLE 21. Pentaerythritol Producers (SRI, 1975)

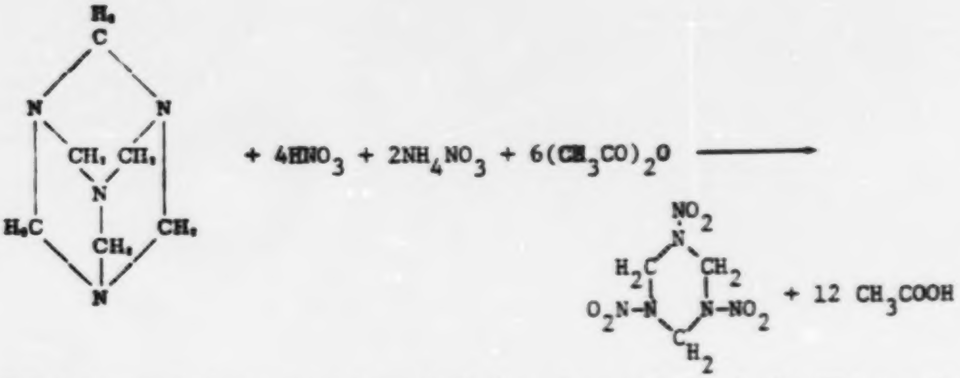
Producer	Location	Capacity Mil. lbs/year
Celanese Corporation	Bishop, Texas	50
Commerical Solvents Corp.	Seiple, Pennsylvania	20
Hercules, Inc.	Louisana, Missouri	40
Pan American Chemical Corp.	Toledo, Ohio	25
TOTAL		135

TABLE 22. Pentaerythritol Production
(U. S. Tariff Commission)

	Year				
	1971	1972	1973	1974	1975
Quantity Produced (Millions of lbs)	88	110	103	125	-

e. Hexamethylenetetramine

Approximately five percent of the formaldehyde produced each year goes into the production of hexamethylenetetramine. The production of this compound was discussed in Section III-A, page 42. Hexamethylenetetramine has two major uses: the production of RDX, and as a thermosetting catalyst in the phenolic resins production. (See Section III-B, page 47.) RDX (cyclonite, trimethylenetrinitramine) is a military explosive which utilizes approximately fifty percent of the hexamethylenetetramine produced. The major military and commercial manufacturer of RDX is Holston Army Ammunition Plant in Kingsport, Tennessee. The Bachmann process is used at this installation (Bachmann, 1949). This process proceeds according to the following equation:



(25)

HMX (tetramethylenetetranitramine) is a by-product of the RDX manufacture.

2. Minor Uses

Formaldehyde has a variety of uses in all aspects of modern society, including agriculture, paper, textile and dyestuffs manufacture, medicine, etc. Table 23 is a compilation of the minor uses of formaldehyde and its products.

TABLE 23. Minor Uses of Formaldehyde and Its Products (Walker, 1975)

Agriculture

1. Treatment of bulbs, seeds and roots to destroy microorganisms.
2. Soil disinfectant.
3. Prevention of rot and infections during crop storage.
4. Treatment of animal feed grains.
5. Chemotherapeutic agent for fish.

Analysis

Small quantities are used in various analytical techniques.

Concrete and Plaster

Formaldehyde is used as an additive agent to concrete to render it impermeable to liquids and grease.

Cosmetics and Deodorants

Formaldehyde is utilized in deodorants, foot antiperspirants and germicidal soaps.

Disinfectants and Fumigants

Formaldehyde is employed to destroy bacteria, fungi, molds and yeasts in houses, barns, chicken coops, hospitals, etc.

Dyes

1. Manufacture of intermediate for production of rosaniline dyes.
2. Preparation of phenyl glycine, an intermediate in the manufacture of indigo dyes.
3. Used to prepare formaldehydesulfoxylates which are stripping agents.

Embalming

Formaldehyde is used in connection with other embalming agents to preserve and harden animal tissue.

TABLE 23 (Continued)

Hydrocarbon Products

1. Prevent bacterial action from destroying drilling fluids or muds.
2. Remove sulfur compounds from hydrocarbons.
3. Stabilize gasoline fuels to prevent gum formation.
4. Modify fuel characteristics of hydrocarbons.

Leather

Tanning agent for white washable leathers

Medicine

1. Treatment of athete's foot and ring worm.
2. Hexamethylenetetramine is used as a urinary antiseptic.
3. Conversion of toxins to toxoids.
4. Synthesis of Vitamin A.
5. Urea-formaldehyde is used as a mechanical ion exchange resin.

Metals Industries

1. Pickling agent additive to prevent corrosion of metals by H_2S.
2. Preparation of silver mirors.
3. Hexamethylenetetramine is used to produce nitrilotriacetic acid and formaldehyde to produce ethylenediaminetetracetic acid. These compounds are excellent metal sequestering agents.

Paper

Formaldehyde is used to improve the wet-strength, water shrink, and grease resistance of paper, coated papers and paper products.

Photography

1. Used in film to harden and insolubilize the gelatin and reduce silver salts.
2. Photographic development.

Rubber

1. Prevent putrefaction of latex rubber.
2. Vulcanize and modify natural and synthetic rubber.
3. Hexamethylenetetramine is used as a rubber accelerator.
4. Synthesis of tetraphenylmethylenediamine, a rubber antioxidant.

TABLE 23 (Continued)

Solvents and Plasticizers, Surface Active Compound

1. Synthesis of ethylene glycol.
2. Synthesis of formals.
3. Synthesis of methylene derivatives.
4. Synthesis of surface active compounds.

Starch

Formaldehyde is used to modify the properties of starch, by formation of acetals and hemiacetals.

Textiles

Modification of natural and synthetic fibers to make them crease, crush and flame resistant and shrink-proof.

Wood

Used as an ingredient in wood preservatives.

3. Discontinued Uses

Formaldehyde in cosmetics and deodorants in the United States has been declining, due to the dermatitis responses in users. The use of formaldehyde or hexamethylenetetramine as a food perservative is prohibited in the United States.

4. Proposed Uses

The number of patents pertaining to the proposed uses of formaldehyde is voluminous. It is difficult to assess from this literature what new products will be made from formaldehyde in the next few years. New final uses of formaldehyde are sure to result from the resins industry, as well as from synthetic organic chemical manufacture.

C. ENVIRONMENTAL CONTAMINATION POTENTIAL

The potential sources for environmental contamination from formaldehyde or compounds which can release formaldehyde, is a direct result of its many uses. In addition, formaldehyde is produced by incomplete combustion processes and as a result of photochemical reactions of hydrocarbons in the environment. These sources of potential environmental contamination are discussed in detail in the following subsections.

1. Emissions from Formaldehyde Production and Associated Controls

Formaldehyde manufactured by the silver catalyst process results in one main source of air emissions, the absorber vent. A survey of plants using the silver catalyst process (Morris et al., 1975a) indicates that the absorber vent stream contains hydrocarbon emissions (See Table 24.) in addition to its major constituents of CO, H_2 and CO_2 as shown in Table 24.

TABLE 24. Absorber Vent Stream Composition - Silver Catalyst Process (Walker, 1975; Morris et al., 1975a)

Component	Volume Percent (Dry Basis)
CO_2	4.8 to 5.5
CO	0.2 to 0.6
CH_4	0.3 to 0.4
O_2	0.3
H_2	20.2 to 17.5
N_2	74.2 to 75.7
	Lb/Lb of 37% CH_2O
Formaldehyde	0 to 0.001
Methanol	0 to 0.004
Methyl Formate	0 to 0.008
Methylal	0 to 0.001

If a typical plant producing 200 million pounds per year of 37% formalin emitted 0.001 lbs of formaldehyde/lbs of 37% CH_2O from the absorber vent, a total of 550 lbs of formaldehyde would be lost each day. At a typical flow rate of ~7000 lbs/hr, the exhaust gas would contain 0.3% formaldehyde. This percentage is well within the human odor threshold which is reported to be 0.5 to 1 ppm (Fassett, 1963; Stern, 1968a). However, since no odor complaints were reported for the plants surveyed by Morris et al. (1975a), it is doubtful that local dispersions of the absorber vent gases contain over 1 ppm of formaldehyde.

Aqueous effluents are also reported at some plants (Morris *et al.*, 1975a). The effluents are treated on-site by biodegradation. This procedure is capable of 100% degradation of formaldehyde and should lead to no off-site water pollution under normal operations. Heavy rains and associated water run-off can lead to overloading of the biotreatment facilities and short-term pollution. However, this case is the exception rather than the rule and does not contribute significantly to emissions from aqueous sources.

Manufacturers of formaldehyde by the metal oxide process also report that the absorber vent is the main source of plant emissions. Typical composition of of the gases from both recycle and non-recycle operations are given in Table 25.

TABLE 25. Absorber Vent Stream Composition - Metal Oxide Catalyst Process (Morris *et al.*, 1975b)

	lbs/1b of 37% CH_2O	
Component	Recycle Operation	Non-Recycle Operation
N_2	1.1735	4.2918
O_2	0.0932	1.0772
CO_2	0.0018	0.0182
CO	0.0170	
Methanol	0.0020	0.0034
Formaldehyde	0.008	0.0092
Dimethyl ether	0.0008	0.007

The metal oxide process gives rise to air emissions, expecially in the absence of recycle operations. The plants report odor complaints both on and off site (Morris et al., 1975b).

The control of absorber emissions for the metal oxide process is not as simple or as cost-effective as for the silver catalyst process. These gases have very little fuel value and subsequently cannot be used for boiler fuel. Water scrubbing is used by one facility surveyed (Morris et al., 1975b). This scrubber has an efficiency of only 66% due to the presence of the water insoluble dimethyl ether in the gases. Combustion of this vent gas would be highly efficient for pollution control; however, the operating cost is high due to the need for additional fuel to support combustion.

In summary, the major source of formaldehyde release from the production processes is the absorber vent emissions. These emissions are low to nonexistent for the silver catalyst process. However, for the metal oxide process, they are relatively high for non-recycle operations. Very little control is employed to curb the metal oxide process emissions.

2. Emissions from Transport and Storage

Information on the quantity of formaldehyde lost during transport and storage is very limited. Formalin solutions are shipped in tank cars, tank trucks, barrels, drums, carboys and bottles. However, due to the high cost of transporting an aqueous solution, less than 40% of the total product produced each year is shipped. This estimate is based upon U. S. Tariff Commission sales figures and the high captive market. (See Section II-A, page 27.) Most storage tanks have vents to bleed excess pressure.

Some loss of formaldehyde from formalin solutions may occur from this source. This loss is expected to be minimal due to the low vapor pressure of formaldehyde above aqueous solutions. This pressure is reported to be only 40 mm Hg at storage temperatures of 80°C (Walker, 1975). Taking all these factors into account, the loss of formaldehyde during transit and storage appears to be minimal.

Paraformaldehyde is shipped in bags, fiber drums, and corrugated boxes (Walker, 1966). Since this compound is known to slowly vaporize to yield monomeric formaldehyde, some losses are possible. These losses, however, are also a minimal source of environmental contamination.

3. Formaldehyde Emissions and Effluents Resulting from Use

a. Effluents from Resins Production

The major source of environmental contamination during resins production is the process water which is removed during the dehydration step. Amino-formaldehyde coating resins and the phenolic novolak resins undergo this step. In a study of the manufacture of these resins, Tracy and Powanda (1972) showed the amount of effluent for each pound of resin varies with the type of formaldehyde starting material. The effluents from the manufacture of five million pounds of each resin projected from the results of this study are compared in Table 26. Examination of Table 26 reveals that the total amount of effluent and the amount of formaldehyde emitted from the manufacturing processes are highly dependent on the starting material. Since effluent monitoring data for resins production

TABLE 26. Effluent Produced by Different Forms of Formaldehyde in Manufacturing Five Million Pounds of Resin
(Tracy and Povanda, 1972)
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	Butylated-Urea Resins				Melamine				Phenolic			
	Total Effluent Mil. lbs.	Effluent Constituents Mil. lbs...			Total Effluent Mil. lbs.	Effluent Constituents Mil. lbs.			Total Effluent Mil. lbs.	Effluent Constituents Mil. lbs.		
		HCHO	BuOH	H_2O		HCHO	BuOH	H_2O		HCHO	Phenol	H_2O
Paraformaldehyde	1.429	.057	.114	1.258	1.000	.040	.080	.880	.847	<.001	.042	.804
Butyl Formcel	1,667	.067	.134	1.466	1.250	.050	.100	1.100	-	-	-	-
50% Formalin	3.571	.143	.286	3.142	3.333	.133	.267	2.933	1.923	<.002	.096	1.825
37% Formalin	5.000	.200	.400	4.400	5.000	.200	.400	4.400	2.778	<.003	.139	2.636

is unavailable, as is exact starting materials and quantities produced with these materials, the amount of formaldehyde emitted into the environment can only be estimated. Referring to Table 17 and 19, the production of urea, melamine and phenolic molding compounds in 1975 was 18,100, 17,600 and 90,000 m tons, respectively, or 39.9, 38.8 and 198.4 million pounds. Using 50% formalin as a starting material, the total amount of effluent from each process would be:

- urea - 28.5 m lbs containing 1.14 m lbs of formaldehyde.
- melamine - 25.9 m lbs containing 1.04 m lbs of formaldehyde.
- phenolic - 76.3 m lbs containing <0.08 m lbs of formaldehyde.

Thus from this rough estimate, the urea-formaldehyde resins manufacture has the greatest pollution potential. It is expected that these streams would be treated before dumping, presumably in a biotreatment facility. Biotreatment facilities using activated sludge organisms can efficiently handle urea-formaldehyde wastes, if proper control is maintained. Biodegradation of melamine-formaldehyde wastes may be possible but evidance of this has not been reported in the literature reviewed. Biodegradation of phenolic wastes is not as easily accomplished. Thus even though the amount of formaldehyde in the effluent is small, the production of phenolic novolak resins may be a major source of release, not only of formaldehyde, but also of phenol.

b. Effluents from Resin Use

Adhesives

Glue made from phenolic and urea-formaldehyde resins is one of the major end uses of formaldehyde manufactured in the Pacific Northwest and the Southeast. Formaldehyde production plants, resin manufacturing plants and plywood producers are usually located near the lumber mills. The resins are formed in water and compounded with fillers, defoamers, etc. to form glue. Phenolic-formaldehyde resin-based glues are mainly used for bonding both interior and exterior plywood. Urea resin-based glues are used for hardwood panels. The major pollution from these glues occurs during washdown of the spreaders and clean up of the glue mixing equipment. A study conducted in 1969 on 158 plywood plants in the Pacific Northwest estimated that 6.2 million gallons per day of waste water were generated from these operations (Bodien, 1969). This waste water was reported to be highly concentrated and toxic to the biota, although no formaldehyde or phenol content was available. The results of this study indicate that the glue wastes were one of the biggest pollution problems in these areas of the the United States. Biotreatment of the phenolic glue wastes was not shown to be effective. Suggestions for curbing the pollution were:

1) use of less wash water.
2) investigation of incineration of these waste streams.

Textile and Paper Industry

Both the textile and paper industries use large quantities of formaldehyde and formaldehyde resins in finishing their products, so that they possess the desired characteristics. The amount of aqueous and gaseous effluents from these processes is unknown.

One of the major concerns over the use of formaldehyde in these industries is the safety of the workers. This concern has resulted from the report that formaldehyde can react with HCl in humid air to form bis(chloromethyl)ether, BCME, according to the following equation (Chem. Eng. News, 1973):

$$2Cl^- + 2CH_2O + 2H^+ \longrightarrow ClCH_2OCH_2Cl + H_2O. \qquad (26)$$

BCME is a strong carcinogen causing lung cancer in rats exposed to 100 ppb in air for several months (Laskin et al., 1971). The possibility exists that BCME could be formed in the textile and paper industries by reaction between the formaldehyde and the chloride catalysts used in many of the processes. Since BCME hydrolyzes rapidly in aqueous solution, the aqueous effluents do not appear to be a source of this carcinogen. Two studies have been undertaken to evaluate the potential for BCME formation in moist air. A study of the gaseous reaction at 40% relative humidity was conducted by Kallos and Solomon (1973). They found no detectable BCME formed at reactant concentrations up to 100 ppm each (detection limit ∿0.5 ppb). The highest BCME concentration reported was 48 ppb for a reactant concentration of CH_2O/HCl of 3,000/10,000 ppm. In contrast to this work, Frankel et al. (1974) reported the following BCME concentrations were formed by reacting varying amounts of CH_2O/HCl for 12 to 24 hours at 40% relative humidity and 26°C.

CH_2O/HCl (ppm)	BCME (ppb)
4,000/40,000	5,000
1,000/10,000	730
1,000/1,000	130
300/300	23
100/100	3
20/20	<0.5

These results differ drastically from those reported by Kallos and Solomon (1973). In a recent study to assess the hazards from BCME in formaldehyde emulsion polymers, Hurwitz (1974) found no evidence of the carcinogen under laboratory or mill conditions. However, Hurwitz recommended that working areas in these mills be monitored to insure worker safety. NIOSH is currently conducting sampling studies at various textile and paper plants to determine the hazards (Marceleno _et al_., 1974) of potential BCME formation.

c. Emissions from Formaldehyde Use

In addition to potential contamination of the environment by industrial manufacturing processes utilizing formaldehyde or its resins as a raw material, other minor uses of formaldehyde can be sources of localized contamination. For example, the use of formaldehyde as a fumigant and soil disinfectant is a direct source of contamination which can be intense if proper precautions are not observed. Embalming and leather tanning are also sources of localized contamination. The quantity of formaldehyde used for these purposes is small (probably <3%). Thus, although these uses could result in severe environmental contamination in localized areas, the total effect on the general environment is negligible in comparison with other sources.

4. Emissions from Disposal

Incineration of plastics and other waste products containing formaldehyde resins is of great concern because of the large volume of these wastes generated each year. Two studies have been conducted to determine the emissions from combustion of urea and phenolic resins. Boettner et al. (1973) utilized a thermogravimetric analyzer to follow the combustion of urea resins in an air atmosphere and a heating rate of 10°C/min. Under these conditions, incomplete combustion is expected to occur. The emissions were analyzed by an infrared spectrophotometer. These emissions were found to contain CO_2, CO, CH_4, NH_3 and CN. Another study conducted at Syracuse University (1973) utilized an 815°C furnace with a 954°C afterburner to determine emissions from urea resin. The emissions from incineration, and their toxicity, were found to vary with the amount of air present and the afterburner temperature. With adequate control of these parameters, no toxic emissions were found. When the urea resin was batch-burned, or without the afterburner, 15 to 20 ppm each of methane, acetylene, ethylene; 3 to 10 ppm acrolein; and 2 to 30 ppm HCN were emitted. An ammonium carbonate fly ash was also found in the emissions. These gases were extremely toxic to plants which were irreversibly dehydrated within a few minutes, probably from cyanide poisoning. Rats showed irritation, respiratory distress, convulsions and death within a five minute period. Thus, the incineration of urea formaldehyde resins, without proper premixing and correct afterburner temperatures, results in toxic emissions. It is not, however, a large source of formaldehyde entering the environment, although the presence of this compound in small quantities has been postulated (Syracuse, 1973). Melamine resin incineration has been studied only briefly. The preliminary results indicate combustion products similar to urea resins.

In contrast to the results of the urea and melamine resins incineration, both the Boettner (1973) and the Syracuse (1973) studies showed that incineration of phenolic resins produces relatively non-toxic emissions. Boettner et al. (1973) report that the major products from incineration of a wood-flour-filled Bakelite® plastic are CO_2, CO, CH_4 and possibly ammonia. The authors also reported that small quantities of cyanide were formed early in the combustion process at low temperatures. Emissions from a piece of the same plastic and a phenolic glue were analyzed after combustion in the furnace described earlier (Syracuse (1973)). The gases contained CH_4, < 10 ppm NH_3, <1 ppm CN, <0.55 ppm nitrite-nitrate and no aldehydes or ketones. Rats and young plants exposed to the furnace gases showed no adverse effects.

5. Inadvertent Production of Formaldehyde in Other Processes

Combustion and incineration processes comprise one of the major sources of formaldehyde emitted into the air in the United States. The combustion processes responsible for these emissions can be classified into those resulting from stationary sources and those from mobile sources.

a. Stationary Sources

The major stationary sources of combustion leading to formaldehyde emissions include power plants, manufacturing facilities, home consumption of fuels, incinerators, and emissions from petroleum refineries. The emissions from the fuels consumed in these stationary sources are summarized in Table 27 and discussed below.

The combustion of natural gas in home appliances and industrial equipment has been reported to yield aldehydes. Stern (1968b) summarized reported aldehyde emissions from these sources. Inspection of Table 27 shows that these emissions range from 2,400 to 58,000 $\mu g/m^3$

Table 27. Aldehyde Emissions From Stationary Sources
(Adapted From Stahl, 1969)

Source	Aldehyde Emissions (as Formaldehyde)	Reference	Total Formaldehyde Emitted Annually (Millions of lbs)
Natural Gas Combustion			19
Natural gas-fired appliances and industrial and commercial equipment			
Bunsen burner	2,400 µg/m^3	Stern, 1968b	
Oven range	13,200 µg/m^3	"	
Water heater, 100 gal	9,600 µg/m^3	"	
Floor furnace	3,600 µg/m^3	"	
Steam boiler (10^7 BTU/hr) (low fire)	6,000 µg/m^3	"	
Industrial burners	58,800 µg/m^3	"	
Boilers and process heaters	0.0028 lb/10^5 BTU	"	
Scotch marine boilers	2,400-8,400 µg/m^3	"	
Fire tube boilers	4,800 µg/m^3	"	
Water tube boilers	3,600-13,200 µg/m^3	"	
75 gal water heater	2,400 µg/m^3	"	
Space heater	2,400 µg/m^3	"	
Bake oven	7,200 µg/m^3	"	
Industrial oven, indirect	3,600-7,200 µg/m^3	"	
Ceramic kilns, indirect	2,400-8,400 µg/m^3	"	
Natural gas (~0.045 lb/ft^3; 1,000 BTU/ft^3)	10 lb/10^6 ft^3 gas	Hovey *et al.*, 1965	
Power plants	1 lb/10^6 ft^3 gas	Weisburd, 1962	
Industrial	2 lb/10^6 ft^3 gas	"	
Fuel Oil			105
Distillate (~ 7 lb/gal)	.28 lb/1000 lb	Hovey *et al.*, 1965	
	(0-2.07)	Wohlers & Bell, 1956	
Residual (~ 8 lb/gal)	.14 lb/1000 lb	"	
No. 2	1.3 lb/1000 lb	"	
Small sources (1000 hp or less)(~8 lb/gal)			
Extreme range	0-3.3 lb/1000 lb	Smith, 1962	
Usual range	0-0.6 lb/1000 lb	"	
Large Sources (1000 hp or more)(~8 lb/gal)			
Extreme range	0-1.2 lb/1000 lb	"	

Table 27. (continued)

Source	Aldehyde Emissions (as Formaldehyde)	Reference	Total Formaldehyde Emitted Annually (Millions of lbs.)
Coal			3.0
Bituminous (27,200,000 BTU/ton)	2 lb/ton	Hovey *et al.*, 1965	
Anthracite (25,200,000 BTU/ton)	1 lb/ton	"	
Bituminous from pulverized fuel of cyclone furnaces	<0.01 lb/ton	Perry & Field, 1967	
Power plants	0.005 lb/ton	Mayer, 1965	
Industrial	0.005 lb/ton	"	
Domestic and commercial	0.005 lb/ton	"	
Incinerators			13.1
Domestic Incinerators			
AGA prototype, USASI domestic wastes	0.8 lb/ton	Stern, 1968c	
AGA prototype, other refuse mixtures	1.2-3.1 lb/ton	"	
New manufacturers' units, shredded paper	0.17-15.9 lb/ton	"	
Older units, USASI domestic wastes	5-6 lb/ton	"	
Domestic incinerator	4.0 lb/ton refuse	Magill, 1956	
Domestic incinerator	1.4 lb/ton refuse	"	
Domestic, Single chamber			
Without auxiliary gas burning	6 lb/ton refuse	Interstate Air Pollution Study, 1966, Mayer, 1965	
With auxiliary gas burning	2 lb/ton refuse	"	
Other Incinerators			
Single chamber	0.03-2.7 lb/ton	Stern 1968c	
Wood waste	1.8 lb/ton	"	
Backyard (Battelle), paper & trimmings	29 lb/ton	"	
Backyard, 6 ft^3, paper	2.1 lb/ton	"	
Backyard, 6 ft^3, trimmings	5.7 lb/ton	"	
Backyard, 3 ft^3, mixed rubbish	5.1 lb/ton	"	
Incinerator, apartment, flue-fed	2.5-7.8 lb/ton refuse	Kaiser *et al.*, 1959	
Commercial and domestic, small and/or single-stage	3 lb/ton refuse (0.1-4.5 lb/ton)	Hovey *et al.*, 1965	

Table 27. (Continued

Source	**Aldehyde Emissions (as Formaldehyde)**	**Reference**	**Total Formaldehyde Emitted Annually (Millions of lbs.)**
Other Incinerators (continued)			
Industrial and commercial, single chamber	5-64 lb/ton refuse	Interstate Air Pollution Study, 1966	
Multiple chamber	0.3 lb/ton refuse (0.14-0.85 lb/ton)	Interstate Air Pollution Study, 1966 & Mayer, 1965	
Apartment, flue-fed	5 lb/ton refuse	Mayer, 1965	
Multiple chamber, experimental	0.008-0.32 lb/ton	Stenburg *et al.*, 1961	
(asphalt, felt roofing, and newspaper)		"	
Oil Refinery			34.1
Catalytic cracking unit			
Fluid	19 lb/1000 bl	Public Health Service, Cincinnati, Ohio, 1960	
Thermofor	12 lb/1000 bl	"	
Boilers and process heaters		"	
Fuel gas	3.1 lb/1000 bl	"	
Fuel oil	25 lb/1000 bl	"	
Compressor internal combustion engines	0.11 lb/1000 bl	"	
	Total Annual U. S. Formaldehyde Emissions from Stationary Sources		174.20

(2 to 49 ppm). Studies of the combustion of natural gas having a rating of 1000 BTU/ft^3 showed the average aldehyde emissions to be 10 lbs/$10^6 ft^3$ of gas (Hovey et al., 1965). Emissions from power plant and industrial plants utilizing natural gas were reported to be 1 lb/10^6 ft^3 and 2 lbs/10^2 ft^3 of gas, respectively (Weisburd, 1962). The low values reported in this study compared to Stern's data may be due to the use of emission control devices.

The amounts of aldehydes emitted from the combustion of fuel oil varies with the grade of the oil and the size, type and operating condition of the oil-fired equipment. Reported values for distillate oil, residual oil, and No. 2 fuel oil are presented in Table 27. These values are for total aldehydes and range from 0 to 3.3 lb/1000 bl. Approximately 60 to 80% of the total aldehyde emissions is formaldehyde.

The use of coal as a fuel for power and industrial plants is increasing. This increase is expected to continue at least in the near future. Therefore, emissions from coal combustion can be a significant factor in air pollution. Aldehyde emissions (probably 90 to 100% formaldehyde) from coal are reported to be <0.01 to 2 lbs/ton for bituminous coal (Hovey et al., 1965; Perry and Field, 1967) and 1 lb/ton for anthracite coal (Hovey et al., 1965). Studies have shown that this emission can be reduced significantly by fly ash collectors, due to absorption of the formaldehyde on the fly ash (Cuffe et al., 1967). The use of ash collectors may be the reason for the more recent finding of 0.005 lbs/ton from power plant, industrial, and commercical sources (Mayer, 1965).

In order to estimate the amount of formaldehyde emitted from the combustion of natural gas, fuel oil and coal, the parameters listed in Table 28 were used.

TABLE 28. Parameters for Computing Formaldehyde Emissions from Fuel Combustion

Source	Avg. Amount of Aldehydes Emitted (as Formaldehyde)	% Formaldehyde in Aldehyde Emissions	1975 Usage (American Pet. Inst.)	Amount of Formaldehyde Emitted Annually
Natural gas	1 lbs/10^6ft^3	100	19.0 x 10^{12}ft^3	19 x 10^6 lbs
Distillate Fuel Oil	0.2 lbs /1000 lbs	70	4.4 x 10^{10} gal	43 x 10^6 lbs
Residual Fuel Oil	0.3 lbs/1000 lbs	70	3.7 x 10^{10} gal	62 x 10^6 lbs
Coal	0.005 lbs/ton	100	1.1 x 10^{12} lbs	3.0 x 10^6 lbs
		TOTAL		127.0 x 10^6 lbs

Thus a total of ~127 million pounds is emitted into the atmosphere each year from the burning of coal, fuel oil and natural gas.

Incineration of wastes has also been shown to be a source of atmospheric aldehydes, principally formaldehyde and acrolein (Jacobs, 1964). The formaldehyde in the emissions increases with decreasing gas temperature, an increase in excess air, and/or decrease in feed rate (Stenburg _et al._, 1961). Average formaldehyde emissions can be estimated to be 60 to 80% of the total aldehydes emitted. The type of incinerator used also influences the aldehyde content of the emissions. As observed from Table 27, municipal incinerators average about 1.1 lbs/ton of refuse (Hovey _et al._, 1965; Mayer, 1965; Stern 1968c). Small domestic incinerators are reported to have aldehyde emissions ranging from 0.1 to 16 lbs/ton (Hovey _et al._, 1965; Stern, 1968c) and backyard incinerators up to 29 lbs/ton (Stern, 1968c). Utilizing the data from municipal incinerators (1.1 lbs/ton) which burn approximately 17,000,000 tons per year (EPA Office of Solid Waste), an estimated value for formaldehyde emissions from this source is 13.1 x 10^6 lbs annually.

A Los Angeles survey (Public Health Service, 1960) showed that aldehydes emitted from petroleum refinery catalytic cracking and thermofor units were 19 and 12 lbs/1000 barrels of feed, respectively. They estimated ∿2.4 tons of aldehydes per day were emitted in Los Angeles from these sources. The total amount of petroleum refined in the United States in 1974 was 4.4×10^9 barrels. If half the aldehydes emitted are formaldehyde, then $\sim 34.1 \times 10^6$ lbs of formaldehyde would be emitted from petroleum refineries annually.

b. Mobile Sources

The main mobile sources of air pollution include automobiles, diesels and aircraft. Of these sources, the automobile is the largest polluter, contributing heavily to local smog conditions. The amount of aldehyde emitted from automobile engines varies with the type of gasoline used, type of engine, condition of the engine (Stern, 1968c) and the engine mode, i.e., acceleration, deceleration, etc. The results of several studies are presented in Table 29. The estimated aldehyde emission rates vary from a low of 3.4 lb/1000 gal of gasoline to a high of 18.7 lbs/1000 gal. Average aldehyde emissions are ∿10 lbs/1000 gal. Of the total aldehydes emitted in automobile exhaust, ∿50 to 70% is formaldehyde (Fracchia et al., 1967; Hurn, 1962).

Aldehyde emissions from diesel engines are estimated to be between 10 and 16 lbs/1000 gal of fuel. (See Table 29.) These emissions lie in the upper range of automobile emissions. The formaldehyde content of these emissions averages between 50 and 70%.

Table 29. Aldehyde Emissions from Mobile Sources (Adapted From Stahl, 1969)

Source	Aldehyde Emissions (as Formaldehyde)	Reference
Automobiles, General		
(1 gal gasoline = 6.25 lb)	3.4 lb/1000 gal gasoline	Wohlers and Bell, 1965
	4 lb/1000 gal gasoline	Chass et al., 1960
	10 lb/1000 gal gasoline	Hovey et al., 1965
	17.5 lb/1000 gal gasoline	Dept. of Public Health, State of Calif., 1955
	18.7 lb/1000 gal gasoline	Magill and Benoliel, 1952
Cruise	3.3 lb/1000 gal gasoline	Scott et al., 1957
Acceleration or deceleration	7.1 lb/1000 gal gasoline	Scott et al., 1957
Diesel Engines		
General		
	2.5 lb/1000 lb fuel	Larson et al., 1953
	10 lb/1000 gas burned	Wohlers and Bell, 1956
	16 lb/1000 gal burned	Hovey et al., 1965
2 Cycle, No. 2 fuel		
500 rpm, no load	0.027 lb formaldehyde/gal fuel	Reckner et al., 1965
1200 rpm, 1/4 load	0.004 lb formaldehyde/gal fuel	"
1600 rpm, full load	0.005 lb formaldehyde/gal fuel	"
Aircraft		
Total operations (below 3500 ft.)		
Jet, 4 engines	4 lb/flight, 6 lb/1000 gal fuel	Interstate Air Pollution Study, 1966 & Mayer, 1965
Turboprop, 2 engines	0.3 lb/flight, 5 lb/1000 gal fuel	"
Turboprop, 4 engines	1.1 lb/flight	"
Piston engine, 2 engines	0.2 lb/flight, 5 lb/1000 gal fuel	"
Piston engine, 4 engines	0.5 lb/flight	"

Data on aircraft emissions based upon fuel consumption is sketchy, since most of the literature data is reported in lbs/day. From the information available, approximately 5 lbs of aldehydes are emitted per 1000 gallons of fuel consumed (Mayer, 1965; Interstate Air Pollution Study, 1966). Approximately 60 to 80% of these aldehydes are expected to be formaldehyde.

In computing total formaldehyde emissions from mobile sources, the data listed in Table 30 was utilized.

TABLE 30. Parameters for Computing Formaldehyde Emissions from Mobile Combustion Sources

Source	Average Amount of Aldehyde Emitted (as Formaldehyde)	% Formaldehyde in Aldehyde Emissions	1975 Usage (American Pet. Inst., 1975)	Amount of Formaldehyde Emitted Annually
Automobiles	10 lbs/1000 gallons	60	1.02×10^{11} gallons	610.0×10^6 lbs
Diesel Engines	10 lbs/1000 gallons	60		
Aircraft Engines	5 lbs /1000 gallons	70	Aviation Jet Fuels 1.59×10^{10} gallons	56.0×10^6 lbs
TOTAL				666.0×10^6 lbs

The total formaldehyde air emissions from stationary and mobile combustion sources in the United States is $\sim$840 million pounds. These numbers are only estimates based upon the available data. The accuracy of these numbers is questionable. However, even with an error of several orders of magnitude, they point to some very definite conclusions:

(1) The amount of formaldehyde escaping from formaldehyde manufacture and use is negligible in comparison to other sources.

(2) The automobile is the primary source of formaldehyde air pollution.

(3) Stationary combustion is also one of the main sources of atmospheric formaldehyde.

6. Inadvertent Production in the Environment

Automobile exhaust is a major source of formaldehyde. In addition to the formaldehyde, the exhaust also contains reactive hydrocarbons and nitrogen oxides. These hydrocarbons can undergo photooxidation reactions in the atmosphere with photooxidants such as ozone, oxygen and nitrogen oxides. These photooxidation reactions involve free radical intermediates in a series of complex processes. Mechanisms by which the photochemical products are formed have been proposed. One such mechanism for the photooxidation of hydrocarbons in the presence of nitrogen oxides has been reviewed by Altshuller and Bufalini (1965). Formaldehyde is one of the major products in this nitrogen oxide-hydrocarbon photooxidant system. The yields of formaldehydes produced by photochemical oxidation of various hydrocarbon-nitrogen oxide mixtures were summarized by Altshuller and Bufalini (1965). These figures are presented in Table 31. Inspection of the table shows that photochemical yields of formaldehyde from the irradiation of olefins are relatively high, typically 0.35 to 0.65.

Evidence suggests that irradiated automobile exhaust chemically resembles the hydrocarbon-nitrogen oxide system. The formaldehyde content of automobile exhaust has been shown to increase threefold upon irradiation

Table 31. Yields of Aldehydes via Photochemical Oxidation of Hydrocarbon-Nitrogen Oxide Mixtures (Altshuller and Bufalini, 1965) Reprinted with Permission

Hydrocarbon	Moles/mole of initial hydrocarbon Formaldehyde
Ethylene	0.35, 0.45 0.32, 0.45
Propylene	0.40, 0.45
1-Butene	0.45, 0.4
Isobutene	0.7, 0.6 0.3-0.45, 0.6 0.6, 0.5-0.7
Trans-2-butene	0.35, 0.35
1,3-Butadiene	0.6, 0.6, 0.5
1-Pentene	0.55
2-Methyl-2-butene	0.5, 0.3
1,3-Pentadiene	0.65
2-Methyl-1,3-pentadiene	0.55
2,3-Dimethyl-2-butene	0.25
Cyclohexene	0.4
2,3-Dimethyl-1, 3-butadiene	0.65
3-Heptene	0.8
p-Xylene	0.15
m-Xylene	0.15
1,3,5-Trimethylbenzene	0.15

(Altshuller and Bufalini, 1965). Thus, automobile exhausts are not only the largest source of atmospheric formaldehyde, but are also the source of the reactants for the further production of formaldehyde via photochemical processes. The exact amount of formaldehyde produced by photochemical processes is not known. The quantity is a variable function of the amount of hydrocarbon auto exhaust, other compounds present in the exhaust, total quantity of exhaust, light intensity, temperatures and pressures. However, a rough estimation of the amount of formaldehyde produced by photooxidation of hydrocarbon vehicular emissions can be made. Assuming ideal conditions for photooxidation, a three-fold increase in formaldehyde could be expected or 2000 x 10^6 lbs/year. However, night time and adverse weather conditions would significantly lower the amount of formaldehyde produced by photooxidation. The overall efficiency of the photochemical formation of formaldehyde is estimated to be 10 to 20%. With this efficiency, approximately 200 to 400 x 10^6 lbs of atmospheric formaldehyde would be produced in the United States each year by photochemical oxidation.

D. CURRENT HANDLING PACTICES AND CONTROL TECHNOLOGY

1. Special Handling

Although formaldehyde is not regulated under the Occupational Safey and Health Administration, there are some recommended special handling procedures for the chemical (Manufacturing Chemists Association, 1960). These recommendations include:

- The pouring or handling of formaldehyde or paraformaldehyde in open containers should be performed under forced draft hoods.

- Large quantities of formaldehyde should be handled in closed equipment.
- Work areas in which the formaldehyde concentration exceeds permissible limits should be entered only when wearing air-line masks or canister-type gas masks. Protective clothing should also be employed. Safety goggles are essential when eye or face protection is necessary.

2. Methods for Transport and Storage

Formaldehyde is transported in tank cars, tank wagons, drums, carboys and bottles. The preferred container is stainless steel, ordinary steel lined with resins or rubber, aluminum or glass. Insulated tank cars are used to prevent cooling, and heating of the cars is often employed. Wooden barrels are sometimes used, but they generally discolor the solution.

Formaldehyde is slightly acidic and therefore it corrodes some metals, and metallic impurities result from storage in these metals. Materials recommended for formaldehyde storage are glass, stoneware, stainless steel, acid resistant enamel, rubber and aluminum. Aluminum exposed to formaldehyde results in some initial corrosion, but the metal surface is soon covered with a resistant film of corrosion products. Aluminum is not recommended for storage of hot formaldehyde solutions due to the increased corrosion effect.

3. Disposal Methods

The recommended methodology for disposal of waste streams of formaldehyde and nascent formaldehyde is biodegradation with activated sludge organisms (Ottinger, et al., 1973).

4. Accident Procedures

a. Spill Removal

In accidents involving formaldehyde spills, only protected workers should remain in the area. The spilled formaldehyde should be washed away with large volumes of water or neutralized with dilute ammonia, followed by flushing with water. Inhalation of paraformaldehyde dust should be avoided, and the spilled polymer washed away.

b. Fire

In the event of a formaldehyde fire, self-contained breathing apparatus, protective goggles, and protective overclothing should be used. The fire can be extinguished with water, dry chemical, alcohol foam, or carbon dioxide. Exposed containers should be cooled with water.

c. Skin Contact

Skin which has been exposed to formaldehyde solution or polymer should be thoroughly washed with cold water. Formaldehyde solution or paraformaldehyde dust splashed in the eyes requires that the eyes be gently flushed or washed with copious quantities of water for at least 15 minutes. An eye specialist should be promptly called.

d. Ingestion

A person who has swallowed formaldehyde should be immediately placed in the care of a physician. The person should be encouraged to drink large amounts of water to dilute the formaldehyde. Vomiting should be induced (finger or warm salt water). Demulcents, such as milk or raw eggs, may be used to alleviate the irritation.

e. Inhalation

An individual exposed to formaldehyde gas should be moved to fresh air, and if the condition is serious, a physician summoned. Warm coffee or tea may be given to the patient. Smelling salts or aromatic spirits of ammonia may be inhaled.

If the person is unconscious from formaldehyde poisoning, nothing should be given orally. He should be placed lying down, preferably on the left side with the head low. Foreign objects should be removed from the mouth (dentures, gum, tobacco, etc.). Artificial respiration may be employed, if necessary. Oxygen with carbon dioxide can be utilized for patients with shallow breathing. A physician should be contacted immediately.

5. Current Controls

Effluent guidelines for air and water discharge are discussed in Section V-A, page 173. Other regulated controls have not been noted in the available literature. However, due to the potential for forming bis(chloromethyl) ether by reaction of formaldehyde and hydrochloric acid, the National Institute for Occupational Safety and Health (1974) has recommended several process changes in the textile industry. These changes include:

- Use of low formaldehyde resins.
- Substitution of nitrate catalysts for the presently used chloride catalysts.
- Better ventilation
- Separate storage areas for catalyst and formaldehyde.

E. MONITORING AND ANALYSIS

1. Analytical Methods

a. Formaldehyde

The industrial importance of formaldehyde both presently and historically has resulted in considerable research effort in the area of analytical methods development. This development has also been accelerated by the need for reliable analytical methods for measurement of formaldehyde as a constituent of photochemical smog and as an aquatic toxicant. These factors and others have led to the development of several new analytical methods offering enhanced sensitivity and greater selectivity in formaldehyde determination. Formaldehyde's high chemical reactivity and the ease with which many of its polymeric forms depolymerize to yield monomeric formaldehyde serve to simplify the number of methods applicable for the quantitative determination of formaldehyde in the presence of other compounds.

Reynolds and Irwin (1948) published one of the first reviews of the more classical chemical methods for formaldehyde determination. Table 32 summarizes the most applicable methods from this study. The only classical chemical methods for formaldehyde determination in current use are sodium sulfite, alkaline peroxide and 2,4-dinitrophenylhydrazine.

Based upon their comparison study, Reynolds and Irwin (1948) selected the reaction of 1,8-dihydroxynaphthalene-3,6-disulphonic acid (chromotropic acid) with formaldehyde as the analytical method of choice. Of all analytical methods for formaldehyde determination, the chromotropic acid method is by far the most widely known and used technique.

Table 32. Comparison of Analytical Methods for Formaldehyde - Historical

Method	Sensitivity	Interferences	Application	References
Sodium sulphite	1.6 x 10^{-7} moles/liter (4 ppm)	aldehydes, ketones (methyl) oxidizing agents	air, aqueous systems	Reynolds and Irwin, 1948
hydroxylamine hydrochloride	3.3 x 10^{-6} moles/liter (8.3 ppm)	ferric salts		Reynolds and Irwin, 1948
mercurimetric		acetaldehyde, organic peroxide	aqueous	
5,5-dimethyldihydroresorinol (methone)		acetaldehyde	aqueous, solid material	
potassium cyanide		aldehydes > 5%	nonspecific	
alkaline peroxide	> 3 x 10^{-6} moles/liter (7.5 ppm)	acetaldehyde	aqueous	Reynolds and Irwin
iodimetric (Romijn)	0.003 mg/liter (2.5 ppm)	organic oxidizers	air	Kersey et al., 1940
2,4-dinitrophenylhydrazine	0.5 ppm	lower aliphatic	air	Stahl, 1969
chromotropic acid		acrolein	air, water	

In general, the method involves the formation of a purple monocationic chromagen which absorbs at a wavlength of 580 mμ. Development of the chromotropic acid procedure is credited to Bricker and Johnson (1945). Nine years later, West and Sen (1956) compared the method with the 2,7-dihydroxynaphthalene colometric product and found the only severe interference to be acrolein. Further improvements in this method were made by Lee (1956) whose principal contribution was to increase the strength of the sulfuric acid used in the procedure resulting in a 10% increase in absorptivity. Chromotropic acid is the official method for analysis of formaldehyde in food and food additives for the American Association of Analytical Chemists (AOAC).

Increasing attention to the role of formaldehyde as a common air pollutant lead to Altshuller's (1960) investigation of the chromotropic acid method for air analysis. In 1964, Altshuller introduced a modification to this method. This modification involves the direct sampling of formaldehyde into the chromotropic acid solution with a corresponding ten-fold increase in sensitivity and an increase in simplicity.

Sawicki *et al*. (1961) introduced the MBTH (3-methyl-2-benzothiazolone hydrazone) test designed for use with paper or spot plate detection of formaldehyde. The authors found that as with chromotropic acid, it was analytically more accurate to draw the air sample directly into the reagent for analysis of air. Sawicki also noted that the most sensitive spot test reagent is 2-hydrazinebenzothiazole. A modification of the MBTH analysis by Cummins and Hauser in 1964 resulted in an increase in sensitivity which easily permits analysis by this technique in the ppb range for ambient air. The modification involved a reduction in the oxidizing agent which results in a decrease in the turbidity.

Colorimetric methods which have been utilized to determine formaldehyde in various media are listed in Table 33. A modification of the Schiff method was introduced by Rayner and Jephcott in 1961. (See Table 33.) This method has a sensitivity of 0.1 μg/ml of collecting solution. For a reasonable sampling period of one hour, this correlates with 5 ppm formaldehyde in air. In this initial modification, acrolein and acetaldehyde were found to interfere significantly. A similar method of analysis was introduced by Lyles et al. (1965) in which pararosaniline was used as the reagent in a Schiff determination. This technique has a sensitivity of 0.01 μg/ml on a continuous analysis bases and is highly specific for formaldehyde.

Barber and Lodge (1963) applied the 2,4-dinitrophenylhydrazine test to the identification of components of auto exhausts. Formaldehyde was quantitatively determined by its characteristic R_f value in basic and neutral solution.

In a recently developed spectrophotometric method, Chrastel and Wilson (1974) reacted tryptophan with formaldehyde to give a colored product. This product absorbs at 575 mμ with detection in the nanomole range.

Table 33. Comparison of Current Analytical Methods for Formaldehyde-Spectrometric

Method	λ_{max} mμ	Range μg/ml	Interference	Applications	References
Chromotropic acid	580	.24-4.0	acrolein acetaldehyde	air, water, food	Bailey and Rankin, 1971
J-acid 6-amino-1-napthol-3-sulfonic	λ excite 470 λ emission 520	0.001-0.2 fluoremetric	acrolein, CH_2O polymers	tissue	Bailey and Rankin, 1971
MBTH	628	0.05-.92	aromatic amines, Schiff bases, azo dyes	water, air	Bailey and Rankin, 1971
ρ-phenylenediamine	485	0.05-2.5	SO_2	air	Rayner and Jephcott, 1961
Schiff (rosaniline)	560	0.1	acrolein, NO_2 acetaldehyde	air	
Schiff (pararosaniline)	560	0.01-0.05	virtually specific	air	Lyles *et al.*, 1965
Nash (acetylacetone, ammonia)	514				Smith and Erhardt, 1975
Tryptophan	575	1-100 manomoles/ml	indoles, heavy metals	tissue, water	Chrastil and Wilson, 1975
Phenylhydrazine	520	.88-15			Stahl, 1969
o-aminobenzaldehyde	440	12-120	aliphatic aldehydes		Stahl, 1969
Phenyl-J-acid	660	.56-13	formaldehyde yielding compounds	air	Stahl, 1969

Siggia and Oles (1974) introduced atomic absorption spectroscopy as a method of determining aldehydes. That is accomplished by Tollen's reagent oxidation to the carboxylic acid. The silver is separated and determined by atomic absorption. Sensitivity for this technique is high, ∿1 to 4 nanomole/ml.

In another recent method development Dowex-50WX8 and Amberlite IRC-50 resins were used to determine formaldehyde by ion exchange. Qureshi et al. (1974) claim a 300 μg/ml detection capability with a high throughput for this method.

Although polarographic determination of formaldehyde is not a recent development, new techniques have lowered the detection limit to the parts per billion range. Whitnack (1975) used single sweep techniques to determine formaldehyde and other organics in domestic water supplies.

In another application of an electrochemical method, Afghan (1975) determined 0.25 μg/liter quantities of formaldehyde by twin cell sweep voltammetry. This technique was adopted by the Canadian Centre for Inland Waters and is their method of choice for analysis of carbonyl compounds.

The determination of formaldehyde by gas chromatography is normally accomplished with a flame ionization detector. However, Dankelman (1976) has approached the problem of analysis of linear oligomers in formaldehyde solutions by silyation with BSTA followed by gas chromatographic separation and analysis by 220 MHz NMR.

Studies have shown that formaldehyde can be a significant interference in the gas chromatographic analysis of low levels of vinyl chloride monomer. Krishen and Tucker (1976) collected vinyl chloride monomer samples using the OSHA charcoal tube method. They found the retention time of vinyl chloride monomer to be 445 sec, while that of formaldehyde was 277 sec (on a Porapak Q column, 100°C, 40 ml/min He flow). Thus, with high formaldehyde concentrations, the vinyl chloride monomer peak could be obscured by formaldehyde.

Slawinska and Slawinska (1975) reported a chemiluminescent method for formaldehyde determination using the Tranty-Schorigin reaction in the spectral range 560 to 580 mμ. They found the chemiluminescent intensity to be linearly proportional to formaldehyde concentration from 10^{-7} to 10^{-2} molar. They also developed a system for formaldehyde determination in water with a detection limit of 1 μg/liter. The Tranty-Schorigin reaction involves formaldehyde, alkaline hydrogen peroxide and gallic acid. The lower detection limit of this technique seems bound only by the signal to noise ratio of the instrumentation and the dark current of the detector.

b. Hexamethylenetetramine

There appears to be no method for quantitative determination of hexamethylenetetramine which is both specific and accurate. Addition compounds with metal salts and derivatives with iodine-iodide and picrate are specific for hexamethylenetetramine; however, these methods do not yield reliable quantitative results.

Hydrolysis of hexamethylenetetramine in acid solution is often used as the basis for quantitative analysis. Formaldehyde can be determined by the methods discussed in the previous subsection. Hydrolysis with excess sulfuric acid

$$C_6H_{12}N_4 + 2H_2SO_4 + 6H_2O \longrightarrow 2(NH_4)_2SO_4 + 6CH_2O \qquad (27)$$

and back titration of the acid with standard sodium hydroxide has also been proposed (Walker, 1975; Slowick and Kelly, 1942). This method suffers from interferences due to acids or bases in the sample and time consuming analysis procedures.

2. Monitoring

a. Monitoring Methodology

The formaldehyde monitoring literature is mainly concerned with detection of the aldehyde as a gaseous component of photochemical smog. Thus the critical portion of the monitoring methodology is the method of sampling. Currently, two methodologies exist for gaseous formaldehyde sampling: the impinger sampler and the charcoal tube.

The impinger sampling method utilizes an absorbing liquid which receives the gaseous or gaseous-particulate sample by high velocity impact of the gas stream into the liquid surface. Impinger sampling is most often accompanied by a chemical or colorimetric determination of formaldehyde. The impingement method has been used in monitoring studies by Altshuller (1961), Rayner and Jephcott (1961), Thorpe (1968), Altshuller (1963), Sawicki _et al_. (1961), and others.

The other current sampling method uses a charcoal tube absorbing medium through which a known air volume is drawn. After sampling is complete, the charcoal tube is flushed with carbon disulfide and a gas chromatographic analysis made of the absorbed compounds. This method is the OSHA-recommended method for aldehydes.

The charcoal tube sampling method has a corollary in the specific reagent tube method. In this method, a semi-selective chemical reagent replaces the charcoal tube. The degree of change in the coloring of the reactant is a measure of the quantity present. This specific reagent tube method suffers from disadvantages, including the following

- interferences
- only semiquantitative
- not repeatable
- no allowance for sampling rate.

Recently several new methods have appeared which may radically alter the philosophy of formaldehyde monitoring. The linking of a gas chromatograph to a mass spectrometer has been applied to vinyl chloride monitoring. It seems reasonable to expect that such a system would easily be capable of monitoring formaldehyde in air. Williams and Palm (1974) evaluated second derivative spectroscopy for the monitoring of several air pollutants including formaldehyde. This method has a sensitivity of 719 ppb formaldehyde in air. Still another spectrometric method was developed by Hrubesh in 1974 with absolute specificity for formaldehyde. This method uses the Gunn-diode microwave spectrometer which is capable of detecting 0.03 ppm formaldehyde within a range of 0.00 to 20.00 ppm. However, the microwave method has several inherent disadvantages including a long response time and high cost.

The most recent addition to formaldehyde monitoring methods is the Laser-Raman technique introduced by Inaba and Kobayasi (1969). The method is based upon the Rayleigh and Mie scattering of the formaldehyde species and the Raman active vibrational modes of the CH_2O molecule. The Laser-Raman technique has received the most attention and improvement over the last ten years. As early as 1969, this technique was capable of detecting 1 ppm at a distance of 5 meters.

b. Atmospheric Monitoring Studies

Altshuller and McPherson (1963) monitored the formaldehyde concentration of the Los Angeles atmosphere during a three month period from September to November, 1961. The data from this study have been condensed into Table 34. The method used in the actual analytical determiantion was chromotropic acid. Examination of this data shows the average formaldehyde concentration to be approximately 0.04 ppm. It is also noted that the formaldehyde concentration increased from 0.04 ppm at 7:00 A.M. to 0.05 ppm at 11:00 A.M. The daily maximum occurred between 7:30 A.M. and 1:00 P.M., while the peak concentration occurred late in the morning.

Analyses by Rayner and Jephcott (1961) for formaldehyde in urban Toronto show the same concentration gradients; high in the morning and late afternoon, and least during the very early hours of the morning.

Another formaldehyde monitoring study in the Los Angeles area was carried out by Scott Research Labs in early 1969. Data compiled from one of their monitoring stations in Huntington Park California (Table 35) clearly shows a pattern of high formaldehyde concentration in the late morning (Figure 11). The lowest formaldehyde concentrations were found

TABLE 34. Formaldehyde Concentration in the Atmosphere of Los Angeles (Altshuller and McPherson, 1963)

Date (all 1961)	Concentration Maximum (ppm)	Concentration Minimum (ppm)
9-25	0.03	0.01
9-26	0.115	0.02
9-27	0.07	0.03
9-28	0.08	0.04
10-2	0.08	0.03
10-3	0.15	0.04
10-5	0.16	0.025
10-9	0.04	0.01
10-11	0.045	0.02
10-12	0.065	0.03
10-13	0.10	0.02
10-16	0.10	0.06
10-17	0.065	0.04
10-18	0.04	0.02
10-20	0.025	0.015
10-23	0.06	0.01
10-24	0.065	0.035
10-25	0.07	0.04
10-26	0.06	0.015
10-27	0.055	0.015
10-31	0.025	0.02
11-1	0.03	0.005
11-2	0.02	0.005
11-3	0.06	0.015
11-7	0.04	0.015
11-8	0.035	0.015
11-9	0.045	0.025
11-13	0.06	0.015
11-14	0.035	0.01
11-15	0.02	0.005

Table 35. Concentrations of Formaldehyde at Huntington Park, California (Scott Research Laboratories, 1969)

Date (all 1968)	Concentration Maximum (ppm)	Concentration Minimum (ppm)
8-27	.038	.023
9-4	.023	.021
9-6	.108	.031
9-10	.054	.011
9-11	.043	.020
9-12	.035	.024
9-13	.028	.020
9-16	.035	.025
9-17	.054	.024
9-18	.034	.019
9-19	.017	.006
9-23	.026	.017
9-24	.020	.016
9-25	.088	.030
9-26	.075	.041
9-27	.065	.026
10-1	.015	.010
10-2	.032	.016
10-3	.012	.012
10-4	.023	.007
10-8	.015	.005
10-9	.012	.002
10-10	.021	.018
10-11	.028	.016
10-16	.038	.020
10-17	.033	.023
10-18	.032	.020
10-21	.076	.020
10-22	.136	.023
10-23	.097	.024
10-24	.050	.030
10-25	.062	.035
10-28	.061	.026
11-1	.018	.005
11-6	.030	.023
11-8	.049	.005

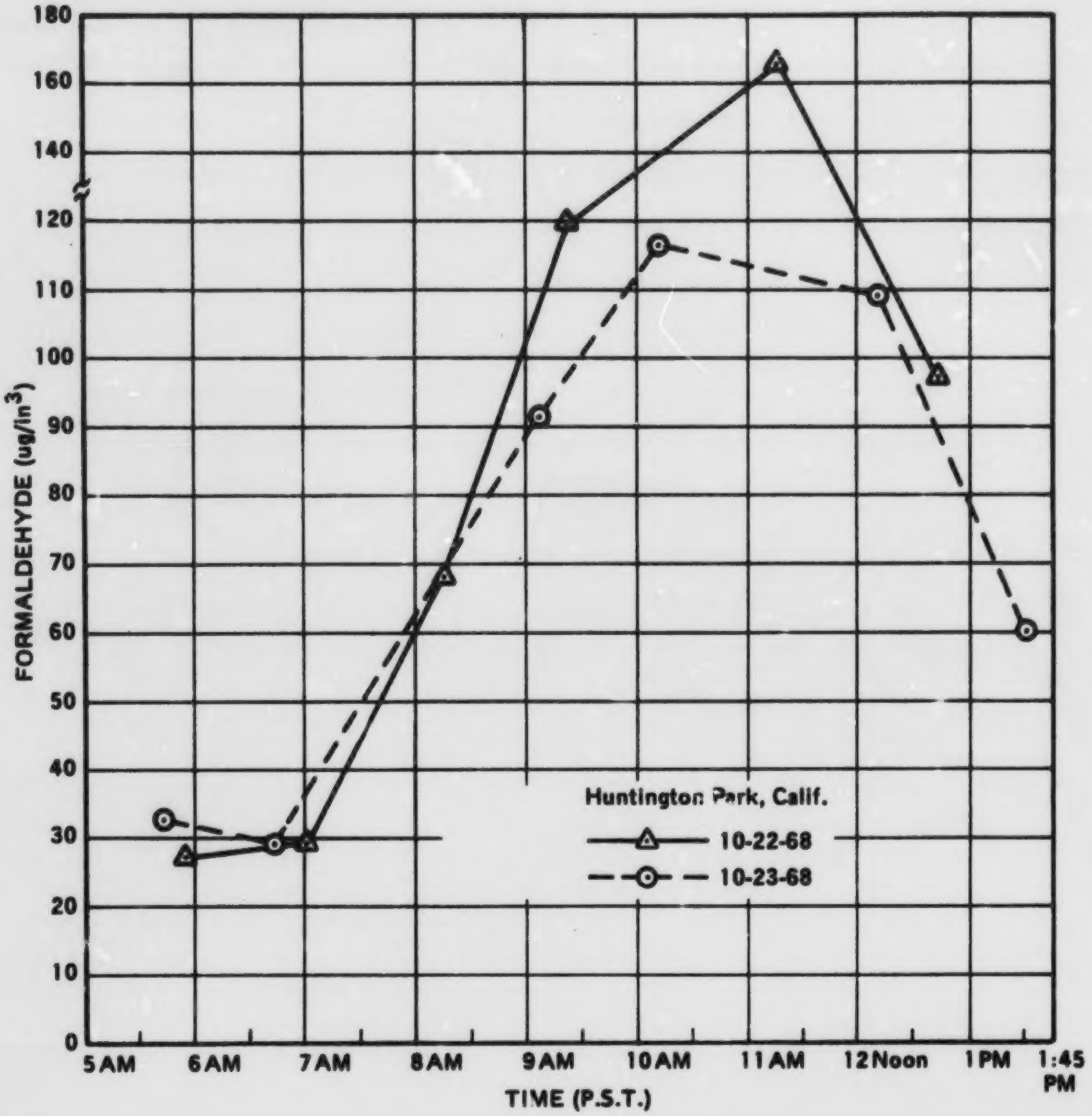


Figure 11. Formaldehyde Concentration in Urban Atmosphere
(Scott Research Laboratories, 1969)

in the early morning before rush hour traffic. During the rush hour, formaldehyde emissions from auto exhausts add to the ambient concentrations. Hydrocarbons also emitted from automobiles during the rush hour are photochemically converted to formaldehyde as the solar radiation increases. Since formaldehyde is also destroyed photochemically, its concentration peaks around 10 to 12 A. M. and then declines.

In contrast to NO_x and SO_2, formaldehyde is not routinely monitored due to the unavailability of a reliable automatic analyzer. The monitoring data found in the literature is thus sporadic. Daily and hourly fluctuations are evident from the data presented in Tables 34 and 35. However, sufficient information is not available to determine the long term trends in atmospheric formaldehyde concentrations.

IV. HEALTH AND ENVIRONMENTAL EFFECTS

A. ENVIRONMENTAL EFFECTS

1. Persistence

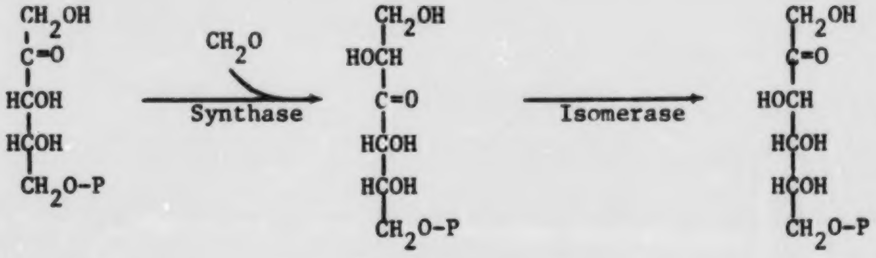
a. Biological Degradation

Even though formaldehyde is often used as a bacteriocide, there are microorganisms which are capable of assimilation of this compound into cell material. In a study conducted at the Warsaw Polytechnic University (1973), certain bacteria in activated sludge were shown to be capable of utilizing formaldehyde as a sole carbon source. These methylotrophic bacteria (bacteria capable of assimilation of methyl compounds - formic acid, formaldehyde, methanol and methane - as their sole carbon source) were identified as various species of Pseudomonas, including Ps. fluorescens, Ps. desmolytica and Ps. ovalis. These bacteria and other similar organisms in activated sludge have proved to be very efficient in degrading formaldehyde in aqueous effluents. Essentially complete degradation is achieved in 48 to 72 hours if proper temperature and nutrient conditions are maintained (Celanese, 1976; Kitchens and Valentine, 1974).

Two pathways for the assimilation of formaldehyde into bacterial cellular material are known:

- ribulose monophosphate cycle
- serine pathway

The ribulose monophosphate pathway was proposed in 1965 as a result of the work of Kemp et al. (Anthony, 1975). The key enzyme involved in the initial incorporation of formaldehyde is hexose phosphate synthase. This enzyme catalyzes the condensation of formaldehyde and ribulose-5-phosphate. A second enzyme, an isomerase, catalyzes the formation of fructose-6-phosphate from the hexulose-6-phosphate:



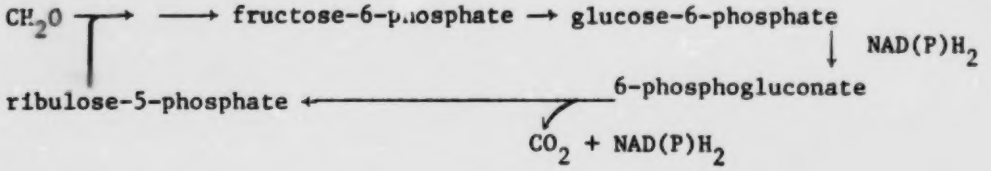
CH2OH
C=O
HCOH
HCOH
CH2O-P
CH2O
Synthase
CH2OH
HOCH
C=O
HCOH
HCOH
CH2O-P
Isomerase
CH2OH
C=O
HOCH
HCOH
HCOH
CH2O-P

(28)

The ribulose-5-phosphate is regenerated by the reactions shown in Figure 12, yielding 3-phosphoglyceraldehyde for use as a cellular biosynthesis substrate. The total reaction is summarized as:

$$3CH_2O + ATP \longrightarrow \text{3-phosphoglyceraldehyde} + ADP \qquad (29)$$

An alternate ribulose-5-phosphate pathway has been suggested by Colby and Zatman (Anthony, 1975) for methylotrophs lacking dehydrogenase for formaldehyde and formate. In this pathway, the formaldehyde is oxidized to CO_2 as shown below.

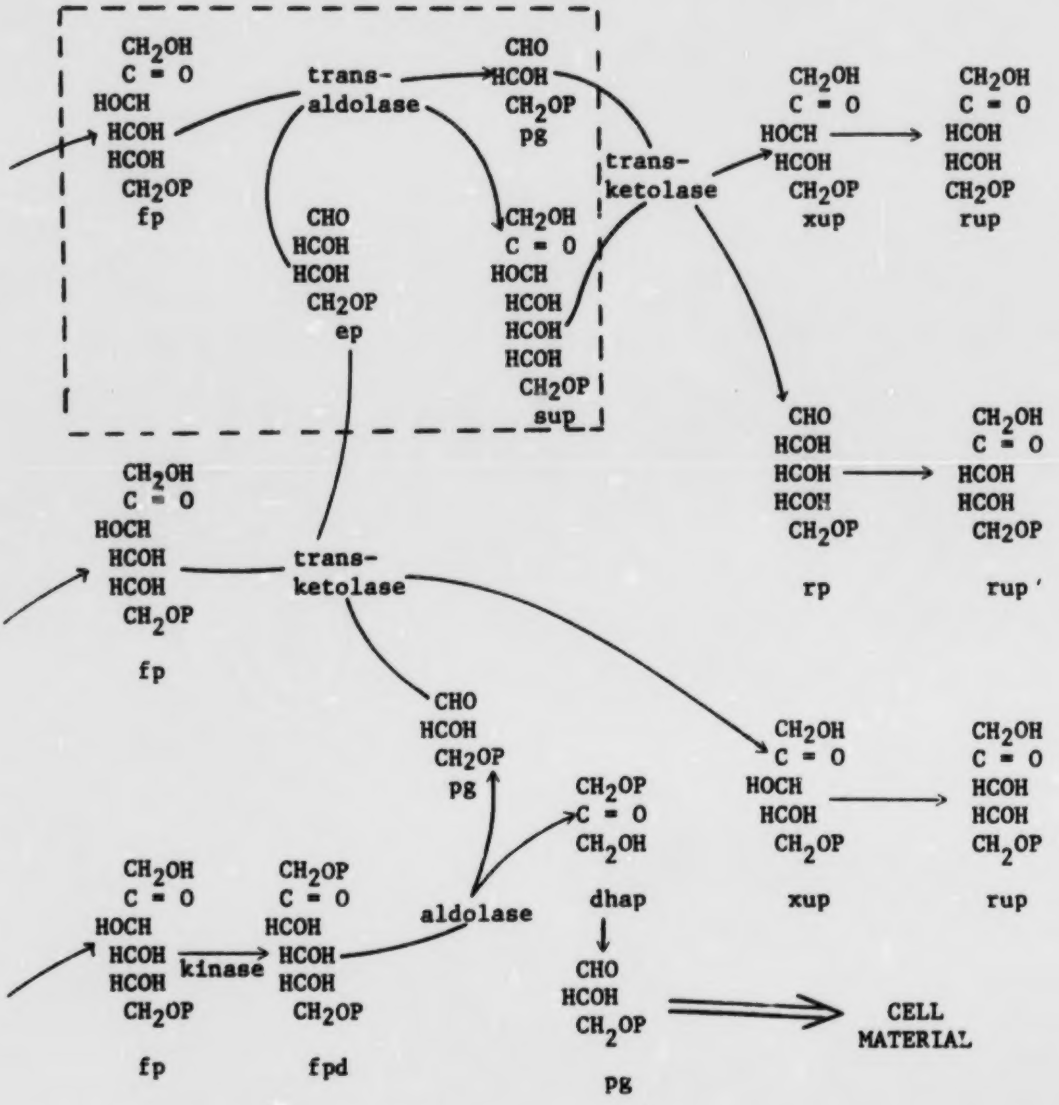


CH2O
fructose-6-phosphate
glucose-6-phosphate
NAD(P)H2
6-phosphogluconate
ribulose-5-phosphate
CO2 + NAD(P)H2

(30)

This cyclic series of reactions utilizes the enzymes synthase, glucose phosphate isomerase, glucose phosphate dehydrogenase, and 6-phosphogluconate dehydrogenase.

The serine pathway is presented in Figure 13. This cyclic pathway affects the addition of formaldehyde (from the methylenetetrahydrofolate) and CO_2 to give one molecule of acetyl CoA. The overall reaction


trans-aldolase
trans-ketolase
trans-ketolase
aldolase
kinase
fp
pg
ep
sup
xup
rup
rp
rup'
fp
pg
dhap
xup
rup
fp
fpd
pg
CELL MATERIAL

ABBREVIATIONS:

fp = fructose-6-phosphate
fdp = fructose-1,6-diphosphate
pg = 3-phosphoglyceraldehyde
ep = erythrose-4-phosphate
dhap = dihydroxyacetone phosphate

xup = xylulose-5-phosphate
rp = ribose-5-phophate
rup = ribulose-5-phosphate
sup = sedoheptulose-7-phosphate
sudp = sedoheptulose-1,7-diphosphate

Figure 12. Regeneration Reactions of the Ribulose Monophosphate Cycle of Formaldehyde Fixation in Methylotrophs (Anthony, 1975)

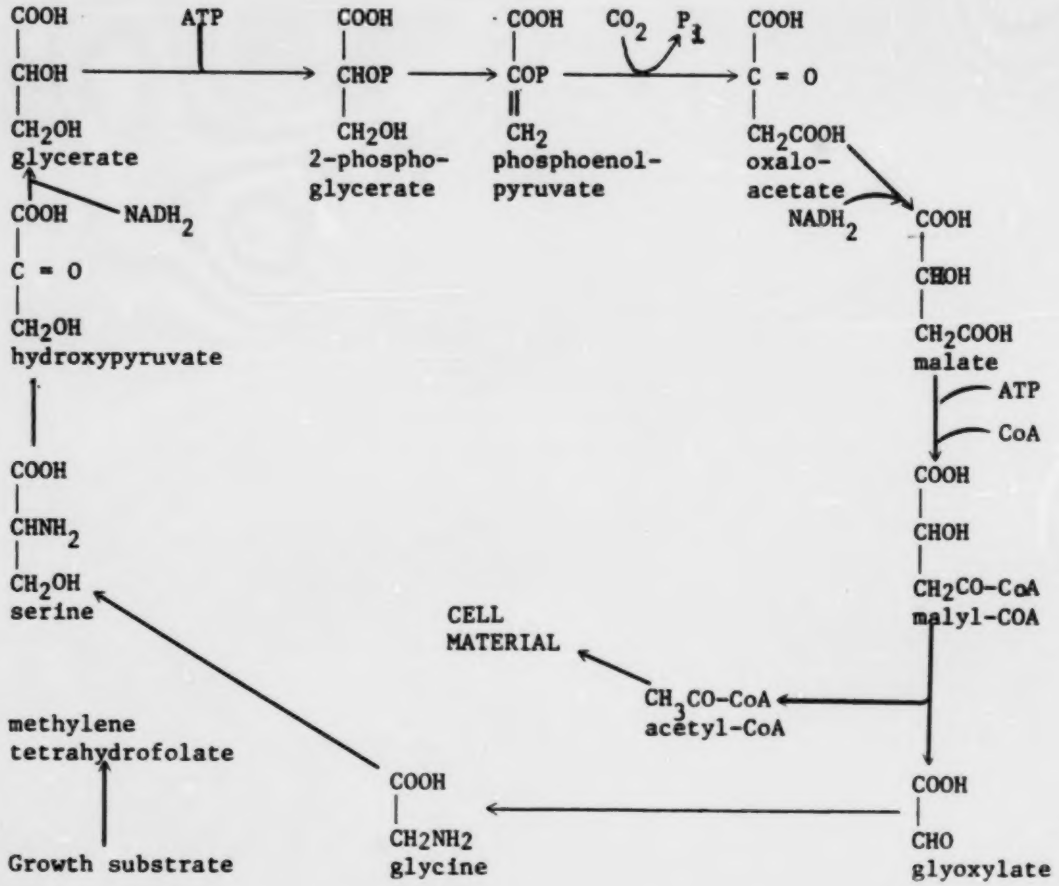

COOH
CHOH
CH2OH
glycerate
ATP
COOH
CHOP
CH2OH
2-phospho-
glycerate
COOH
COP
CH2
phosphoenol-
pyruvate
CO2
Pi
COOH
C = O
CH2COOH
oxalo-
acetate
NADH2
COOH
CHOH
CH2COOH
malate
ATP
CoA
COOH
CHOH
CH2CO-CoA
malyl-COA
CH3CO-CoA
acetyl-CoA
CELL
MATERIAL
COOH
CHO
glyoxylate
COOH
CH2NH2
glycine
methylene
tetrahydrofolate
Growth substrate
COOH
CHNH2
CH2OH
serine
COOH
C = O
CH2OH
hydroxypyruvate
NADH2

Figure 13. Serine Pathway for Methylotrophic Growth (Anthony, 1975)

can be expressed as:

$$CH_2O + CO_2 + CoA + 2NADH_2 + 2ATP \longrightarrow CH_3CO_2\text{-}CoA + 2NAD + 2ADP + 2P_i + 2H_2O \quad (31)$$

The acetyl-CoA thus formed is further incorporated into cellular material.

Only one study on the biological degradation of aldehydes in natural waters was encountered. In this study, Kamata (1966) measured the vertical distribution of formaldehyde in stagnant lake water (Lake Kezaki in Japan). He found that aldehydes were only found in detectable concentrations in the hypolimnion. Samples of the lake water were returned to the laboratory to demonstrate formaldehyde decomposition. Under aerobic conditions, known quantities of added formaldehyde were decomposed in ~30 hours at 20°C. Anaerobic decomposition took ~ 48 hours. No decomposition was noted in sterilized lake water. Aldehyde contents of sea water were also measured by Kamata (1966), no aldehydes were found in surface waters.

b. Chemical Degradation

Formaldehyde and nascent forms of formaldehyde can undergo several types of reactions in the environment including depolymerization, oxidation-reduction and reaction with other air and aquatic pollutants. Air contaminants from commercial processes likely to be found in the vicinity of formaldehyde producers or users include ammonia, chlorine, hydrogen chloride and solvents such as alcohols and ketones. Possible water pollutants which could be prevalent in areas where formaldehyde is found in aqueous effleunts include phenols, urea, ammonia, metal ions, hydrochloric acid, nitric acid, sodium bisulfite, etc.

i. Depolymerization Reactions of Paraformaldehyde and Trioxane

Paraformaldehyde slowly hydrolyzes and depolymerizes as it dissolves in water to yield aqueous formaldehyde solution. Paraformaldehyde dust can enter the atmosphere during processing and handling. This dust slowly depolymerizes to yield formaldehyde.

Trioxane, in contrast to paraformaldehyde, has more chemical and thermal stability. Depolymerization would not be expected from normal chemical reactions in the atmosphere. It is also inert under aqueous neutral or alkaline conditions. Dilute acid solutions show slow depolymerization. Thus, slow depolymerization to formaldehyde in aqueous acidic solution would be the expected environmental reaction.

ii. Oxidation-Reduction Reactions

Formaldehyde is a reducing agent, itself being oxidized to formic acid. Oxidation-reduction reactions in the environment can occur with metal ions and other easily reduced compounds. This reaction is not expected to lead to any compounds of significant hazard potential from effluents of the industries investigated.

iii. Reactions with Other Pollutants

The reaction of formaldehyde with ammonia quantitatively produces hexamethylenetetramine, however, the small quantities of the two constituents which would be found together in the environment preclude any significant formation.

Formaldehyde and hexamethylenetetramine react with hydrogen chloride to yield bis(chloromethyl)ether. Much concern has been expressed over this reaction because of the carcinogenicity of the ether. This reaction is not a problem in aqueous solutions or effluents due to the rapid hydrolysis of the ether. Thus, the equilibrium for the reaction lies far to the left

$$2HCl + 2HCHO \leftleftharpoons ClCH_2OCH_2Cl + H_2O \qquad (32)$$

and no bis(chloromethyl)ether is found within the 9 ppb detection limits (Tou and Kallos, 1974). In air at 40% relative humidity, Frankel et al. (1974) have reported the formation of 3 ppb bis(chloromethyl)ether from 100 ppm each of hydrogen chloride and formaldehyde. In contrast, Kallos and Solomon (1973) found less than 0.1 ppb of bis(chloromethyl)ether.

The problem of bis(chloromethyl)ether formation in the industrial or general environment is at this time unresolved. Further carefully controlled experiments and on-site monitoring are needed before any definite conclusions can be drawn as to the seriousness of the problem. The rapid hydrolysis of bis(chloromethyl)ether in aqueous solutions raises the question as to whether carcinogenic activity is actually produced by the ether itself. It is possible that the observed carcinogenicity may be the combined effect of the irritating ability of hydrochloric acid and the alkylating ability of the formaldehyde produced in the hydrolysis reaction. If this postulation is correct, then it may be possible to produce the same effects by alternate exposures to hydrogen chloride and formaldehyde.

Reactions of formaldehyde with phenols, urea or other organics in the environment is possible, but is not expected to result in significant levels of hazardous compounds.

In pulp mill effluents the sodium bisulfite and the formaldehyde effluents would be expected to react to form the formaldehyde bisulfite addition product.

$$CH_2O + NaHSO_3 \longrightarrow HOCH_2\ NaSO_3 \cdot H_2O \text{ and } (HOCH_2\ NaSO_3)_2 \cdot H_2O \qquad (33)$$

With nitric acid, oxidization of formaldehyde to CO_2 and water is expected to occur in the environment. (Walker, 1975).

One potentially hazardous reaction of formaldehyde with an inorganic compound is the reaction with chlorine gas in the presence of light.

$$2Cl_2 + CH_2O \xrightarrow[\text{light}]{} COCl_2 + 2HCl \qquad (34)$$

The highly toxic phosgene gas is formed. The extent of occurrence of this reaction is unknown. However, in areas where chlorine gas is emitted in small amounts and can contact atmospheric formaldehyde, this reaction could be of significance. It may be even more significant in an industrial environment utilizing chlorine gas.

iv Photochemistry

The absorption spectra of gaseous monomeric formaldehyde shows three absorption bands in the ultraviolet region. A weak, long wavelength band lies in the near ultraviolet with $\epsilon_{max} \sim 18$ liters/mole/cm at λ_{max} 304 mμ. This absorption band, which results from a symmetry forbidden $n \rightarrow \pi^*$ transition, is shown in Figure 14. Two intense bands lie in the vacuum ultraviolet with λ_{max} at 175 and ~ 160 mμ. However, it is the weak absorption at 304 mμ which is responsible for initiating photochemistry in formaldehyde in the lower atmosphere. Primary photochemical reactions in the lower atmosphere

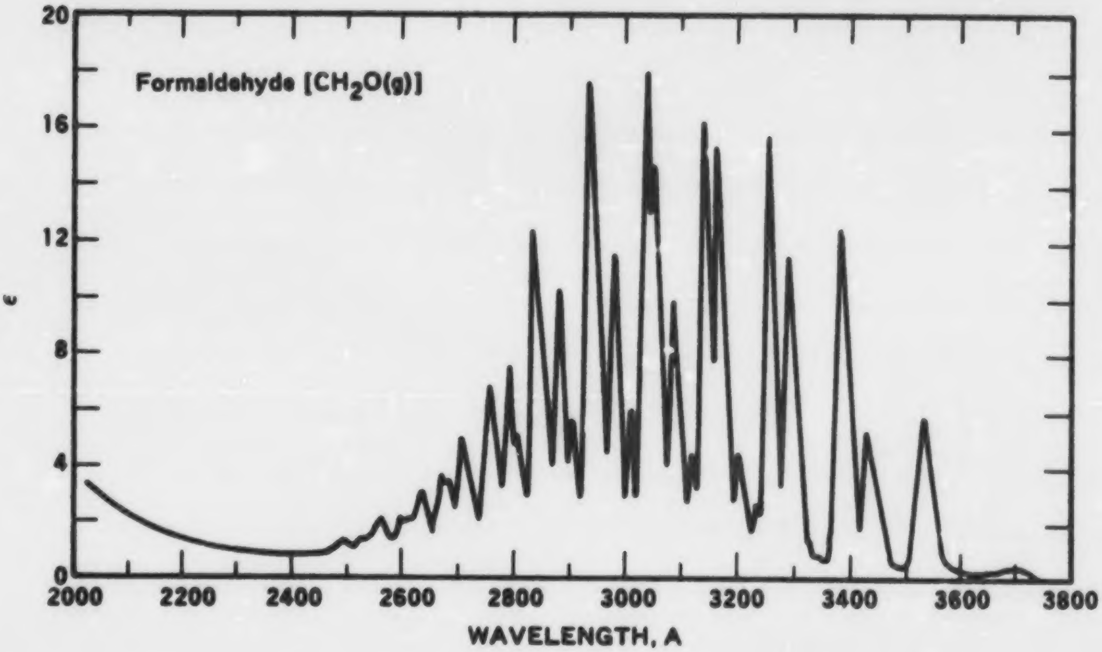


Figure 14. Absorption Spectra of Formaldehyde (Calvert and Pitts, 1967) Reprinted with Permission

occur only when the compound shows absorption at wavelengths greater than 290 mμ. The limitation is due to the ability of the earth's atmosphere (mainly the ozone layer) to completely filter out all radiation of shorter wavelengths than 290 mμ.

The primary photochemical reactions for formaldehyde have been shown to be

$$CH_2O + h\nu \longrightarrow H + HCO \qquad (I) \qquad (35)$$

$$\searrow H_2 + CO \qquad (II) \qquad (36)$$

Process I is important at all wavelengths of excitation. Process II is only important for excitation wavelenghts shorter than 313 mμ (Calvert and Pitts, 1967). Thus process I is the primary process in the lower atmosphere. Once formed, the H and HCO radicals undergo a variety of reactions to form many products depending on the conditions.

With high formaldehyde concentrations Carruthers and Norrish (1936) found formic acid, CO, CO_2, H_2 and a polymer to be the photochemical products of formaldehyde. Different observations have been made when the formaldehyde concentration was low. Under these conditions H_2O_2 is formed (Purcell and Cohen, 1967; Bufalini et al., 1972). However, in the presence of NO_2, the peroxide is not formed in a high concentration. The rate of product formation from the photochemical degradation of formaldehyde on the presence and absence of NO_2 is shown in Figure 15. These processes have been postulated to be the dominant source of H_2O_2 in the atmosphere (Bufalini et al., 1972).

Inspection of Figure 15 shows that the half-life of formaldehyde in the absence of NO_2 is approximately 50 minutes; in the

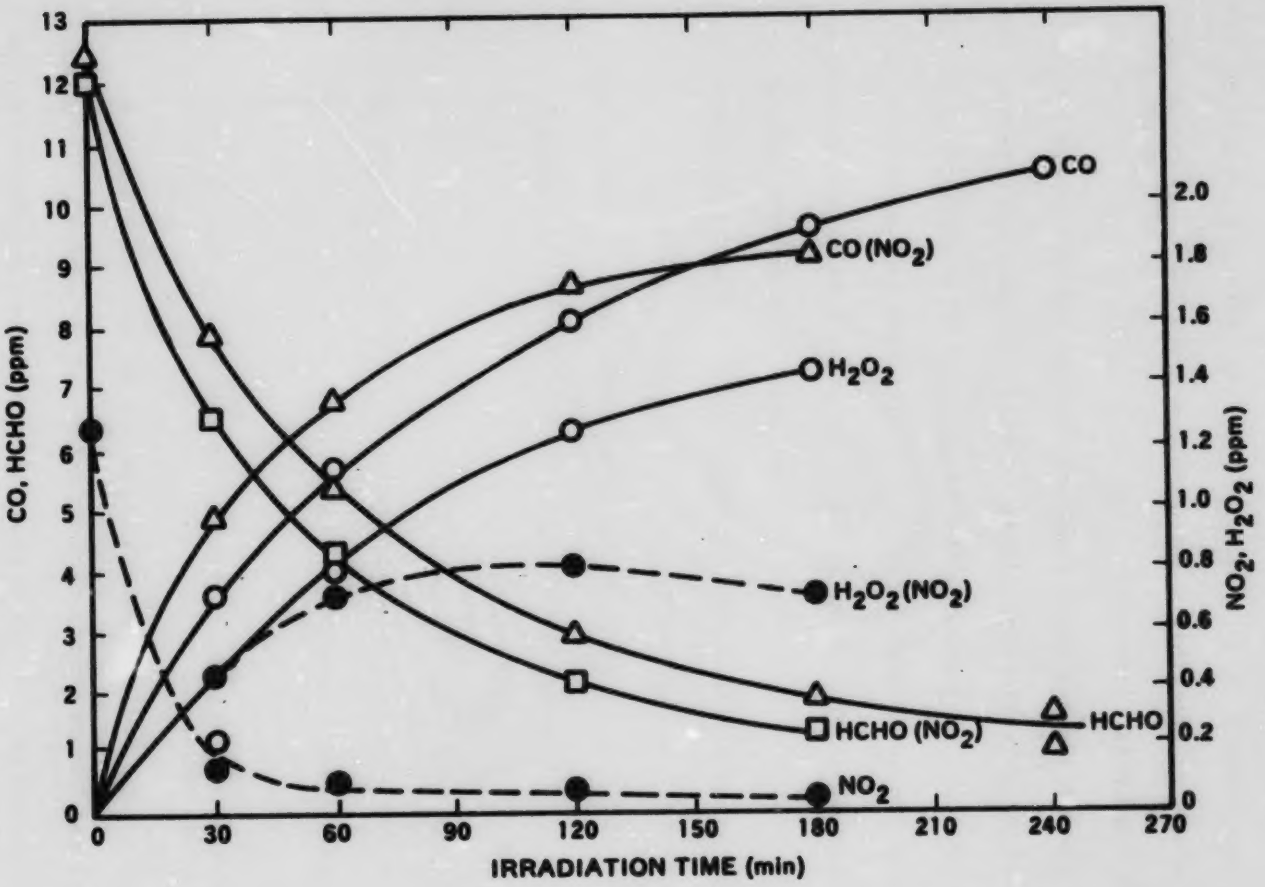


Figure 15. Formaldehyde Irradiated with and without NO$_2$ in the Presence of Sunlight (Bufalini et al., 1972)
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presence of NO_2 this drops to ~ 35 minutes. Thus, an efficient mechanism exists for destruction of atmospheric formaldehyde.

2. Environmental Transport

Formaldehyde gas is transported through the atmosphere by wind currents. During this transport, it is continually undergoing photodecomposition if sunlight is present. Due to its high water solubility it is also washed from the atmosphere by rain. Formaldehyde concentrations in rain water were determined by Shearer (1969). Concentration ranges from 0.31 to 1.38 mg/l were reported. However, the values were at the lower end of the sensitivity of the analytical method (phenylhydrazine) and thus there is some question as to their accuracy.

Formaldehyde is also transported in waterways. However all evidence points to its rapid biodegradation, if the biota in the natural waterways are not overloaded.

3. Bioaccumulation and Biomagnification

Formaldehyde is a natural metabolic product and is not subject to bioaccumulation and biomagnification.

B. Biology

1. Absorption, Transport, Metabolism and Elimination of Formaldehyde

The normal routes by which formaldehyde can enter the body are through dermal and occular contact, inhalation and ingestion. On dermal contact formaldehyde reacts with the active hydrogen in the protein molecules of the skin resulting in crosslinking and precipitation of the proteins. Under repeated mild exposure, an allergic skin rash occurs in sensitive persons. More severe exposure conditions result in hardening and tanning of the skin due to coagulation necrosis. Most cases of dermatitis are caused by contact with aqueous formaldehyde solutions or clothing containing formaldehyde although incidents have also been reported for vapor contact. The literature reviewed did not cover any studies on the depth of penetration of formaldehyde into living tissue. However, formaldehyde penetration in meat carcasses up to 30 mm deep has been reported (Monroe *et al.*, 1924). Presumably similar penetration depths could occur in living tissue. Formaldehyde vapors and solutions cause severe eye burns. Prolonged exposure to low concentrations of the vapors can also result in irritation and inflamation of the eyelids.

Inhalation of formaldehyde vapors produces irritation and inflammation of the bronchi and lungs. *In vitro* studies of the action of aqueous formaldehyde on lung tissue showed that the tissue properties were altered, possibly by forming intermolecular crosslinkages (Sigihara and Martin, 1975). This mechanism probably also occurs *in vivo* leading to lung damage. Once in the lungs, the formaldehyde vapors can be picked up by the blood stream.

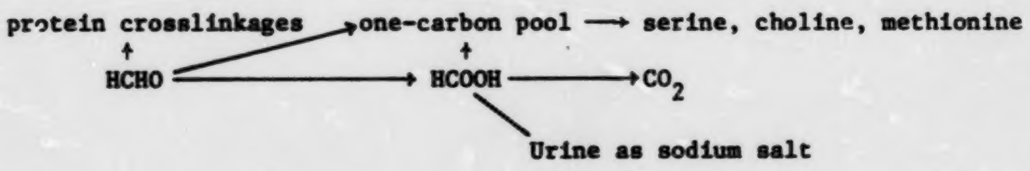
Ingestion of formaldehyde is followed immediately by inflammation of the mucosa of the mouth, throat, and gastro-intestinal tract. Absorption appears to occur in the intestines (Malorny *et al.*, 1965). Once absorbed into the blood stream, formaldehyde disappears rapidly. This rapid disappearance is due to condensation reactions with body tissue constituents such as proteins, and oxidation is formic acid. Since formaldehyde is a normal metabolite of most living systems, it is not surprising that minor quantities can be rapidly handled by mammalian systems. The main reaction appears to be initial oxidation to formic acid followed by further oxidation to CO_2 and H_2O. This pathway was shown to occur when rats were fed ^{14}C labeled formaldehyde. In this study, 40% of the ^{14}C was recovered as respiratory CO_2 (Buss et al., 1964). The intraperitoneal application of ^{14}C formaldehyde to rats resulted in 82% of the dosages expired in the air as CO_2. Studies on the metabolism of methanol, for which formaldehyde is an intermediate, have shown the presence of several enzymes capable of catalyzing the oxidation of formaldehyde to formic acid. Westerfield (1955) identified six different enzymes capable of catalyzing this conversion: aldehyde dehydrogenase, glyceraldehyde-3-phosphate dehydrogenase, aldehyde oxidase, xanthine oxidase, catalase and peroxidase. Strittmatter and Ball (1955) isolated a formaldehyde specific, NAD-dependent formaldehyde dehydrogenase from beef liver. This enzyme requires the presence of reduced glutathione. Similar formaldehyde dehydrogenase enzymes have been found in the liver of other mammals, including humans.

The liver and the erythrocytes appear to be the sites for the rapid oxidation of formaldehyde to formic acid. Malorny et al. (1965) showed that human blood rapidly oxidized formaldehyde to formic acid after adsorption on erythrocytes in vitro. Matthies (1957a, b; 1958) found aldehyde dehydrogenase present in the erythrocytes was responsible for catalyzing this reaction. In vivo studies in dogs and cats also showed a rapid appearance of formic acid in the plasma (Malorny et al., 1965). Once formed, formic acid can undergo any one of three reactions to final detoxification:

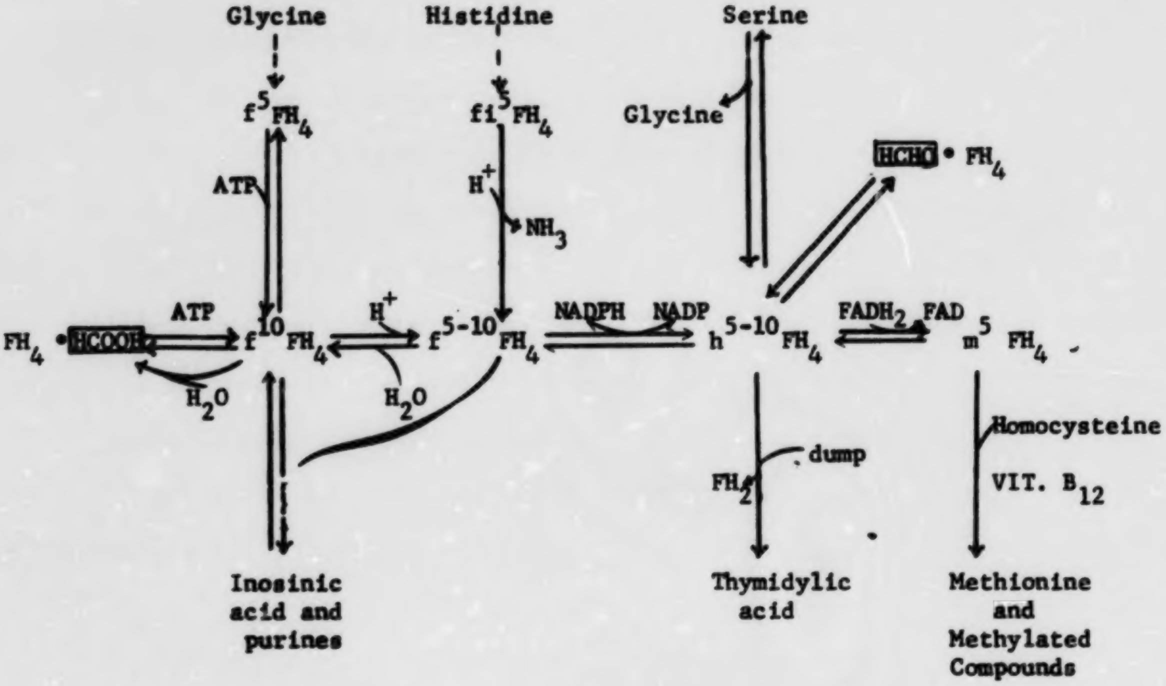
- oxidation to CO_2 and H_2O and exhalation of the CO_2 from the lungs.
- elimination in the urine as sodium salt.
- entry into the one carbon pool.

The one carbon pool is a synthetic pathway which accomplishes the addition of a single carbon group to a substrate molecule. The entry into the pool is accomplished by combination with tetrahydrofolic acid which acts as the methyl donor in the pool. The carbon atom is thus utilized for synthesis of the methyl group of choline or methionine (Berg, 1951; Du Vigneaud et al., 1950) or for synthesis of the β-carbon of serine (Alexander and Greenberg, 1955). The current view of the synthetic mechanism of this pool is shown in Figure 16. This pathway was confirmed by intraperitoneal injection of ^{14}C formaldehyde in rats. Approximately 13 to 14% of the ^{14}C was recovered in methionine, serine and an adduct of cysteine in the urine (Holmberg and Malfors, 1974).

The metabolic pathway for formaldehyde can be summarized:



This pathway is capable of handling minor quantities with relatively little difficulty. However, large doses overload the detoxification mechanism resulting in acidosis and tissue damage from protein crosslinkages.


Glycine
Histidine
Serine
f5 FH4
fi5 FH4
Glycine
HCHO • FH4
ATP
H+
NH3
FH4 • HCOOH
ATP
f10 FH4
H+
f5-10 FH4
NADPH
NADP
h5-10 FH4
FADH2
FAD
m5 FH4
H2O
H2O
Homocysteine
dump
FH2
VIT. B12
Inosinic acid and purines
Thymidylic acid
Methionine and Methylated Compounds

FH_4 - tetrahydrofolic acid

$f^{10}FH_4$ - N^{10}-formyltetrahydrofolic acid

f^5FH_4 - N^5-formyltetrahydrofolic acid

$f^{5-10}FH_4$-N^5, N^{10}—methylnyltetrahydrofolic acid

fi^5FH_4 - N^5-formininotetrahydrofolic acid

$h^{5-10}FH_4$ - N^{10}-methylenetetrahydrofolic acid

Figure 16. One Carbon Pool
(Koivusalo, 1956; 1970)

2. Pharmacology of Formaldehyde

The local action of formaldehyde is the coagulation of proteins. Because of this ability, formaldehyde is a recognized protoplasmic poison. The cytotoxicity of formaldehyde was studied by using Ehrlick-Landschutz diploid (ELD) ascites tumor cells during short time in-vitro incubations. Holmberg and Malfors (1974) found that formaldehyde was highly toxic to ELD cells at a concentration of 100 ppm after 1 hour incubation and with 50 ppm after a 2 hour incubation. The frequency of irreversibly injured cells at the end of 5 hours incubation did not increase remarkably compared to the frequency at the 1 and 2 hour incubations.

From a systemic point of view, formaldehyde causes a decrease in blood pressure and irregular respiration (Akaban, 1970; Skog, 1950). Intravenous injection of formaldehyde into anesthetized rats was investigated by Egle and Hudgins (1974). At dosages of 5 mg/kg or less, formaldehyde evoked primarily a pressor response. At 10 mg/kg, both pressor and depressor effects were seen with about equal frequency. At 20 mg/kg a depressor response was seen exclusively. The pressor response appears to be the result of catecholamine release from sympathetic nerve endings and from the adrenal medulla. This hypothesis was confirmed by use of agents and/or procedures which altered sympathetic activity. Doses less than 20 mg/kg formaldehyde did not alter heart rate. However at 20 mg/kg, marked bradycardia with occasional transient cardiac arrest was observed. This effect was diminished by atropine and abolished by vagotomy.

Kensler and Battista (1963, 1970) have shown formaldehyde to be ciliatoxic and to inhibit ciliary transport in the respiratory system.

Carson et al., (1966) showed that formaldehyde produced mucostatic effects in vivo using intact cat trachial systems. Retention of inhaled formaldehyde vapor (0.15 to 0.35 mg/ml) was almost 100% throughout the entire respiratory tract of dogs regardless of ventilation rate, tidal volume and concentration inhaled (Egle, 1972). The response of lung function to formaldehyde inhalation in both tracheotomized and normal animals has been studied by several investigators (Amdur, 1960; Davis et al., 1967; Murphy and Ulrich, 1964). An increase in flow resistance and tidal volume and a decrease in respiratory rate were observed by Amdur (1960) in both normal and tracheotomized animals. Davis et al. (1967) observed the opposite responses in tracheotomized animals, namely a decrease in total volume and an increase in respiration rate. This finding was attributed to the by-pass of the response receptors in the upper airway in the tracheotomized animals.

Several Russian investigators (Bonashevskaya, 1973; Guseva, 1973; Bokina and Ekslar, 1973; Fel'dman and Eksler, 1975) have shown that the inhalation of formaldehyde vapor will affect the central nervous system causing electrophysiologic behavioral and histologic changes. The major areas that have been evaluated are the olfactory bulbs and amygdala.

In rabbit eyes formaldehyde induced chemical irritation consists of ocular hypertension, increased protein leakage and miosis (Cole, 1974). Other miscellaneous effects of formaldehyde include:

(a) Prolongation of the Q-T interval of dog electrocardiograms following direct perfusion of the S-A node. Ventricular fibrillation also resulted. No significant sympathomimetic activity was observed (James and Bear, 1968).

(b) Sterilization of male goats by causing mild to moderate damage to the semeniferous tubules and interstitium was observed after scrotal instillation of 10 ml of a 4% solution (Sharma et al., 1973).

3. Therapeutic Use of Formaldehyde and Hexamethylenetetramine

The ability of formaldehyde to react with proteins is the basis of its use in converting toxins to toxoids. The formaldehyde reacts with the protein and blocks the free amino group by conversion to methylene compounds. The resulting cross-linkages lead to a loss of toxicity and conversion to a toxoid without any major alteration of antigenicity. The relatively non-toxic toxoids are used for inducing immunity.

Intravesical instillation of formalin is utilized to control intractable hemorrhagic cystitis which often follows radiation therapy. Reports of the results of this type of treatment have ranged from minimal complications to bladder rupture and death. Rankin (1974) examined the bladders of young rats after intravesical injection of 1 to 10% formalin. The injection of solution of 5% or greater resulted in death of the animals. Bladders in the treated animals were distended, thickened and adhered to surrounding structures. No histological examinations were reported for non-lethal doses. In studies with dogs, Whittaker and Freed (1975) confirmed the action of formalin to be precipitation of cellular protein on the mucosa of the bladder and a fixative action on small capillaries. Histological and microscopical examinations of the bladder tissue at 1 week, 1, 2, 6 and 12 months after instillation showed initial disruption of the urothelium which gradually returned to normal appearance in 6 to 12 months. The authors recommend that intravesical instillation of formalin should be used only when more conservative measures fail.

Hexamethylenetetramine (methanamine) is absorbed from the intestinal tract and is transported through the body unchanged. It is rapidly excreted in the urine. If the urine is acidic, hexamethylenetetramine breaks down into formaldehyde and ammonia. This release of formaldehyde is the basis for use of methenamine as a urinary antiseptic. As a urinary antiseptic, it is often combined with an acidic moiety such as mandelic or hippuric acid. Methanamine is particularly useful in treatment of chronic urinary infections caused by gram-negative organisms such as Escherichia coli.

Methenamine hippurate is tolerated when given orally with only occasional gastro-intestinal intolerances reported (Seneca, 1967). There has been no reported evidence of liver damage, bone marrow depression or peripheral neuritis with the recommended dosage. With an excessive dosage, gastro-intestinal irritation and bladder irritation occur from the higher concentration of formaldehyde. Andelman (1965) studied over 300 pregnant women with bacteriuria treated with methenamine hippurate and found that no toxicity was experienced. Children subsequently born experienced no abnormalities (Andelman, 1965). Riker Laboratories (1964-65) confirmed the low toxicity of methenamine hippurate in studies in rats, rabbits and dogs. No teratogenic effects were found. Gibson (1970) evaluated methenamine hippurate in 29 cases of urinary tract infections. Only two of the twenty-nine patients experienced side effects such as nausea when given 2 gram doses daily for four weeks. No other side effects were reported. Gerstein et al.

(1968) studied the effects of methenamine hippurate in the treatment of chronic urinary tract infections. Eighteen patients were involved in this study, and received 4 gm · daily doses for up to 16 months. Five of the 18 patients experienced possible adverse reactions. Two patients experienced nausea and vomiting on 4 grams per day, but were able to tolerate 2 gms per day. One patient experienced nausea but returned to normal without any change in the drug dosage. One patient developed an erythematous rash which disappeared. Another patient developed a rash 6 weeks after treatment initiation and lineup continued until the drug was discontinued.

An accidental overdose of methenamine mandelate was reported by Ross and Conway (1970). A 2½ year old boy ingested at least 8 gms of the drug and developed hemorrhagic cystitis. The patient recovered completely without specific treatment.

In addition to its use as an urinary antiseptic, hexamethylenetetramine has also been reported to be effective in treatment of acute phosgene poisoning. The action of hexamethylenetetramine appears to be the combination with the active CO group of phosgene to prevent progressive pulmonary edema (Stavrakis, 1971).

C. Toxicity - Humans

1. Epidemiology

a. Physiological Effects of Formaldehyde Vapors on Humans

The general physiological effects observed when a human being is exposed to non-lethal doses of formaldehyde vapors are irritation of the mucous membranes of the eyes, nose and upper respiratory tract. Skin irritation may also be observed in sensitive individuals (Manufacturing Chemists Association, 1960; Fassett, 1963; Sax, 1975). The level of irritation and resulting symptoms are a function of the formaldehyde concentration and the sensitivity of the individual. The variability of individual responses to gaseous formaldehyde is evident from a review of the thresholds reported in the literature. These values are summarized in Table 36. In general, the irritation threshold lies around 1200 $\mu g/m^3$ (1 ppm) which is also reported to be the odor threshold (Fassett, 1963). However, odor thresholds as low as 70 $\mu g/m^3$ have been reported in highly sensitive individuals (Melekhina, 1960, 1962). Most persons can tolerate 2-3 ppm (2400-3600 $\mu g/m^3$) without any apparent effects or discomforts. Above this level, the discomfort to the individual becomes pronounced. Symptoms include coughing, sneezing lacrimation, dyspnea, feeling of suffocation, headache, increased pulse, fluctuations of body temperature and weakness. Exposure to high concentration ($> 60,000$ $\mu g/m^3$ or 5 ppm) can cause damage to the respiratory tract. Bronchitis, laryngitis and possibly bronchopneumonia may result. Damage to eyelids is also observed at concentrations greater than 60,000 $\mu g/m^3$.

The wide utilization of formaldehyde in a variety of industries as well as its occurrence as an air pollutant has prompted several studies on effects of formaldehyde on man. Specific occupational studies

Table 36. Responses of Man to Various Concentrations of Formaldehyde Vapors (Stahl, 1969)

Concentration µg/m^3	Concentration ppm	Exposure Time	Response	Reference
12	.01		Eye irritation threshold	Schuck et al., 1966
70	.06		Odor threshold	Melekhina, 1960; Melekhina, 1962
80	.07		Chronaximetric response threshold	"
98	.08		Cortical reflex threshold	"
156-540	.13-.45		Irritant threshold	Bourne and Seffrin, 1959
300-6000	.25-5.0		Irritant threshold	Roth and Swenson, 1957
600	.5		Odor threshold	Stern, 1968a
1000	.8		Slight irritation	Meleklina, 1960
1080-1920	.9-1.6		Irritant threshold	Morrill, 1961
1200	1.0		Odor threshold	Fassett, 1963
2400-3600	2.0-3.0	8 hr	Tolerable; mild irritation of eyes, nose, and posterior pharynx	"
4800-6000	4.0-5.0	10-30 min	Intolerable to most people; mild lacrimation; very unpleasant	"
6000	5.0		Throat irritation threshold	Walker, 1975
12,000	10.0	few min.	Profuse lacrimation	Fassett, 1963
24,000	20.0	15-30 sec	Lacrimation	Barnes and Speicher, 1942.
24,000	20.0	30 sec	Irritation of nose and throat	"
24,000	20.0	1-2 min	Sneezing	"
60,000-120,000	50-100	5-10 min	May cause very serious damage	Fassett, 1963
16,560	13.8		TCLo	Sim and Pattle, 1957

will be presented in the next Section (IV-C page 128). This section will discuss general studies of the effects of formaldehyde on humans.

The most noticeable symptom of smog conditions is eye irritation (Hamming and MacPhee, 1967). In 1960 Renzetti and Schuck found that formaldehyde and acrolein produced by the photooxidation of hydrocarbons were a major cause of eye irritation from smog. A year later, Renzetti and Bryan (1961) reported a correlation between the concentration of formaldehyde in smog and the intensity of eye irritation. In further studies using simulated atmospheric chambers, Schuck et al. (1966) found that linear correlations between formaldehyde concentration and intensity of eye irritation did not hold below 360 $\mu g/m^3$ (0.3 ppm). The human eye was found to detect and respond at the same level to formaldehyde concentrations ranging from 12 $\mu g/m^3$ to 360 $\mu g/m^3$.

In studies by Fel'dman and Bonashevskaya (1971), the olfactory threshold for formaldehyde was investigated using human subjects aged 17 to 44. Four formaldehyde concentrations were used, ranging from 90 to 54 $\mu g/m^3$. This study showed that formaldehyde at a concentration of 73 $\mu g/m^3$ was detected by 7 of the 15 test subjects. The subliminal concentration was 54 $\mu g/m^3$. Electroencephalograph (EEG) observations were conducted using 5 subjects shown to be the most sensitive from the olfactory threshold determinations. Formaldehyde concentrations of 53 and 40 $\mu g/m^3$ were tested. Concentrations of 53 $\mu g/m^3$ produced reliable changes in the cerebral electric activity in all the subjects. A concentration of 40 $\mu g/m^3$ exhibited no effect on cerebral bioelectric activity.

Another Russian worker (Sgibnev, 1968) measured the nervous system response for concentrations of 1000 $\mu g/m^3$ and 300-400 $\mu g/m^3$ of formaldehyde. Eleven people were subjected to 14 tests which included EEG, galvanic skin reaction, ECG, respiration and winking frequency. He found an orientation reaction, olfactory sensation and irritation of the upper respiratory tract upon exposure to 1000 $\mu g/m^3$. Accelerated breathing and ECG changes were also noted at the exposure level. Exposure levels of 300-400 $\mu g/m^3$ resulted in an orientation reaction in most subjects and an olfactory response in half of the subjects. No significant EEG changes were recorded.

The level of formaldehyde exposure which produces significant EEG response differs by a factor of 10 in the two Russian studies (Fel'dman and Bonashevskaya, 1971, Sgibnev, 1968). Sufficient information on experimental methodology and collected data is not available to evaluate the results of the two studies. Additional well controlled human exposure studies to low concentrations of formaldehyde (< 1000 $\mu g/m^3$) are necessary to establish the subtle effects of this chemical on the body.

b. Dermatitis

In addition to its effects on the respiratory and central nervous system, formaldehyde in both aqueous and vapor forms causes dermatitis. Dermatitis from exposure to formaldehyde is a common problem in industrial workers who contact this chemical on a daily basis. Specific case studies will be discussed in Section IV-C, page 128. Dermatitis reactions are also being observed in the general public with the use of formaldehyde resins in a variety of consumer products such as textiles, paper, etc.

Marcussen (1959) studied 249 cases of formaldehyde contact dermatitis between 1934 and 1958 and noted that 26 cases or 10.8% of them were caused by textile formaldehyde dermatitis. Hovding (1961) in a study of 69 patients with positive patch test formaldehyde allergy, recorded a high incidence of textile dermatitis caused by formaldehyde. Forty-five of the 69 patients with clinically verified formaldehyde reactions had clothing dermatitis. All were female. The criteria used to determine the relevance of the patch test response included a characteristic localization of the dermatitis to the peripheral parts of the axillae, the antecubital region, the neck, and upper parts of the trunk, corresponding to the outline of the underwear. Nine of these patients with clothing dermatitis due to formaldehyde allergy were retested to varying aqueous dilutions of formaldehyde from the 0.1% level or 1000 ppm to 4% (40,000 ppm). Of importance is that six of the nine gave positive reactions down to the 0.1% level. Wereide (1964) reported 218 cases of dermatitis caused by allergy to formaldehyde in clothing. Female patients were affected three times as frequently as male patients. Cronin (1963) recorded 30 patients with textile dermatitis due to formaldehyde allergy out of a total of 69 positive formalin patch test reactors. She used 2% aqueous formalin as the patch test antigen.

In 1962, Fisher et al., noted the frequency of reports of formaldehyde textile dermatitis from abroad, especially from the Scandinavian countries in contrast to the scarcity of such reports from the United States. They published information obtained by communication with U. S. manufacturers of textiles, which stated that U. S. fabrics so identified contained no more than 0.075% (750 ppm) of free formaldehyde. These authors were unable to reproduce formaldehyde dermatitis in 20 patients known to be allergic to formaldehyde by having them wear clothes made of these textiles. The presence of formaldehyde in these materials was confirmed by qualitative, not quantitative, analysis. Fisher et al. concluded that the discrepancy between the frequency of reports of textile dermatitis in Scandinavia as compared with that in the United States resulted from the fact that textiles in Europe and Scandinavia contained a relatively higher quantity of formaldehyde. O'Quinn and Kennedy (1965) demonstrated contact dermatitis due to formaldehyde in American textiles in a study of their patients with a history of dermatitis.

The threshold level of free formaldehyde in clothes that will produce clinical dermatitis in a formaldehyde-allergic patient is unknown. From the study by Fisher et al. (1962) it appears that dermatitis occurs when more than 0.075% or 750 ppm of formaldehyde is present in clothing. Berrens et al. (1964), after quantitatively assaying clothing from the Netherlands, arbitrarily advised their patients not to wear those articles of clothing that contained more than 0.05% (500 ppm) of free formaldehyde. On the basis of studies of formaldehyde content of American made clothing (Schorr et al., 1974), it is apparent that the amount of free formaldehyde varies with type of cloth and can be far in excess of the quantities reported by Fisher et al. (1962).

Black (1971) reported a patient with contact dermatitis from formaldehyde in newsprint that contained 0.02% free formaldehyde or only 200 ppm. A 48-hour patch test in this patient was positive to both the newsprint and to 2% aqueous formaldehyde. Horsfall (1934) showed that a 1 part in 8 million concentration of formaldehyde could produce allergic reactions. Therefore, it seems possible to have patients so extremely allergic to formaldehyde as to react to concentrations well below those noted by Fisher et al. (1962).

Clinically it is not uncommon to encounter allergic eczematous contact dermatitis in a distribution highly suggestive of drip dry or wrinkle resistant clothing dermatitis (Fisher, 1973). Often it is difficult to obtain positive patch test reactions with the fabric. Formaldehyde resin dermatitis may not be reproduced by patch testing because contributory factors, such as prolonged contact, sweating and friction are absent. However, it is often possible to detect low levels of free formaldehyde in cloth treated with the formaldehyde resin. This usually dissipates with washing. In many cases, the allergen in the formaldehyde resin is not the formaldehyde moiety of the molecule (Gaul, 1967; Engel and Calnan, 1966).

c. Ingestion of Aqueous Formaldehyde

The ingestion of acute doses of aqueous formaldehyde solutions leads to almost immediate inflammation, ulceration and coagulation necrosis of the mucous lining of the gastrointestinal tract (Gaal, 1931). Circulatory collapse and kidney damage follow soon after ingestion, leading to collapse and death. It has been estimated that the lethal dose in man ranges from 1 to 2 oz. of 37% solution. Deaths from as little as 1 oz within 3 hours (Kline, 1925) and recovery from as much as 4 oz. (Kline, 1925) have been reported. Chronic studies of ingestion of 22 to 200 mg/day for 13 consecutive weeks have been reported to result in toxic effects (Zurlo, 1971).

In general formaldehyde ingestion is the result of poisoning or suicidal attempts. However, low levels of formaldehyde can be ingested in food. These levels are either present naturally in the food or are the result of contamination. An important source of contamination is melamine dishware. Tsuchiya _et_ _al_. (1975) have shown that certain foods, namely acidic foods, can elute formaldehyde from this dishware. This effect and its contribution to the daily oral intake of formaldehyde requires further study. An important aspect of any further studies of oral ingestion of formaldehyde should also take into account simultaneous inhalation, since a summation effect has been observed in animals (Guseva, 1973).

The first noted case of formaldehyde poisoning was reported in 1899 by Bock. By 1925 (Kline, 1925) twenty-seven cases of formaldehyde poisoning had been reported. Twelve of these patients died within 20 or 30 minutes to four weeks. The amount of ingested formaldehyde varied from a few drops to 89 cc of concentrated solution. One patient recovered after ingesting 120 cc of concentrated formaldehyde solution.

Kline (1925) reviewed the case histories of the fatal poisonings. The most notable post mortem observations were changes in the esophagus and stomach. These organs showed changes ranging from a simple hardening of tissues to extreme corrosion of tissues. Marked congestion, edema and hemorrhage were frequently present.

Ely (1910) described the case of a three year old boy who drank a few drops of a 40 percent formaldehyde solution. The child immediately experienced coughing and choking which ceased after a short time period. The patient was treated and soon behaved in a normal manner. The child, on the following day, was found to be suffering with a cough and labored breathing. Pulse and temperature were normal and the child reported to be in perfect health. The patient was treated, with temporary improvement. Fifteen hours later the patient was cyanotic and indicated signs of laryngeal obstruction. The patient was again treated, with temporary improvement, but subsequently died. A post mortem showed a thickening of the mucous and submucous coats of the epiglottis and trachea and a superficial necrosis of the trachea.

2. Occupational Exposure Studies

The general use of formaldehyde and its product resins in many industrial facilities has resulted in a large number of occupational exposure studies on this chemical. These studies have been concerned with

- use of formaldehyde as a preservative or fumigant
- manufacture and use of formaldehyde resins.

The incidence of inhaled formaldehyde formalin fumes by two hospital staff members was reported by Hendrick and Lane (1975). These workers were diagnosed as suffering from occupational formalin asthma. The symptoms began between two and four hours after exposure to spilled formalin. Both patients recovered completely when they were removed from formaldehyde vapors.

Kerfoot and Mooney (1975) conducted a study on workers in funeral homes. Air samples in six funeral homes were taken and analyzed. Formaldehyde ranges from a low of 0.09 to a high of 5.26 ppm were recorded. The particle size of paraformaldehyde powder in these air samples was also determined and found to be 1.6 μ. This size is reported to be optimum for deposit and retention of particles in the lungs. Some cases of upper respiratory tract irritation and dermatitis were found among the embalmers. It was recommended that strict standards for embalming room ventilation be set.

At least one case of respiratory distress has been reported for workers engaged in histological preparations (Porter, 1975). However, it was not determined whether the illness was an acute chemical pneumonitis due to formaldehyde or a hypersensitivity reaction in an individual known to be sensitive to allergens.

Workers in a textile mill were exposed to formaldehyde vapors in concentration from 2 - 10 ppm shortly after reporting to work (Ahmad and Whitson, 1973). Ten female employees lost consciousness and were transported to a hospital and regained consciousness. All patients experienced headache and nausea, dizziness and some vomited. All patients recovered.

Several Russian investigations have been conducted to evaluate subtle effects of formaldehyde on the central nervous system and body biochemistry. In a study of a Russian sheepskin drying factory, Kamachatnov and Gayzzova (1971) studied the thermal assymmetry of personnel working in the formalin department. Formaldehyde inhalation as it affected 99 women workers between the ages of 25-40 was studied. A control group consisted of 84 women workers free of formaldehyde vapor. Skin temperature was measured on the forehead, chest, and forearm for a period of two days. Measurements were taken before work, before and after lunch break and at the end of the work day. Skin temperature variations of the right side and left side of the body are shown in Table 37. The table shows that the incidence of physiological asymmetry of exposed workers was 43.3% and pathological asymmetry increased from 48.4% before work to 60% after work.

Shumilina (1975) studied the menstrual and child-bearing functions of Russian women in contact with formaldehyde-urea resins. These women exhibited a menstrual disturbance, prevalent complications during pregnancy and a high percentage of underweight children.

Sources of odor and eye irritation in the plastic injection molding industry were investigated by Clary (1970). Resins such as melamine-formaldehyde, urea formaldehyde, Celcon® and Delrin® were found to undergo localized thermal decomposition as a result of processing. The major constituent of the thermal decomposition was found to be formaldehyde. Recommendations were made for proper ventilation in these industries to avoid worker exposure to formaldehyde.

Engel and Calnan (1966) described an outbreak of dermatitis in a car assembly factory. Fifty workers who handled the para-tertiary butyl phenol (PTBP) formaldehyde resin type adhesive were affected. About 150 operators were involved with the PTBP resin adhesive during the report period. However, the exact number at risk is not known due to the mobility of the workers on the assembly line. Fifty patients were patch tested and 35 (70%)

Table 37. Difference in Skin Temperature Between the Two Sides of the Body (% of total number of observations) (Kamachatnov and Gayzzova, 1971)

Temperature Variation, °C	Workers Exposed to Formalin		Control Group	
	before work	After work	Before work	After work
	Forehead			
0.1-0.5	50	35	28.3	33.5
0.6-2.2	40	65	-	8.0
No variation	10	-	71.7	58.5
	Chest			
0.1-0.5	35	40	26.4	33.0
0.6-2.2	55	50	3.8	8.9
no variation	10	10	69.8	58.1

Temperature Variation, °C	Workers Exposed to Formalin		Control Group	
	Before Work	After Work	Before Work	After Work
	Forearm			
0.1-0.5	25	25	26.4	37.3
0.6-2.2	50	65	5.7	8.9
No variation	5	10	67.9	53.8
	Overall			
0.0-0.5	43.3	33	27.2	34.5
0.6-2.2	48.4	60	3.0	8.6
No variation	8.3	7	69.8	56.9

reacted to the adhesives. These patients were then further patch tested with the resins from the adhesives, and 32 (65%) reacted to one resin type and 29 to the other resin type. It was evident that both adhesives contained sensitizing phenol-formaldehyde resins.

The general consensus from the occupational exposure studies is that adequate ventilation must be provided in industries working with formaldehyde or its resins. Most reporters expressed the opinion that the TLV for industrial exposure was too high. In the United States, OSHA has recently lowered the limit to "not to exceed 2 ppm". According to Russian work, adverse effects are present at levels of 1 ppm. If these findings can be corroborated, then the present level should be reduced further. There is therefore an urgent need for well regulated studies to further quantify the effects of low formaldehyde concentrations on the human central nervous system and the body biochemistry.

D. Toxicity to Mammals

1. Acute Toxicity

Animals administered high dosages of formaldehyde orally, by inhalation or by subcutaneous injections exhibit initial hyperactivity. Rapid eye blinding and rubbing of the face are also observed in gaseous exposure studies. Subsequently, the animals become listless and respiration becomes slow and deep. This is followed by tachypnea, convulsions, opistotonus (back arching), violent respiratory distress and paralysis which results in the death of the animal (Akabane, 1970). Cause of death is functional injury to the respiratory tract (Egle, 1972; Coon et al., 1970; Salem and Cullumbrane, 1960; Sterner, 1963). The histological findings after death show hemorrhages and intra-alveolar and peri-vascular edema in the lungs. The kidney and liver also show hyperemia. With oral administration, hyperemia of the gastrointestinal tract is also observed.

The available data on acute formaldehyde toxicity is summarized in Table 38. In general this data predates 1950. There are a few recent studies which are described below. Skog (1950) conducted formaldehyde subcutaneous injection studies with rats and mice, and inhalation studies with rats. None of the animals died during the inhalation experiments (30 minutes in duration); most of the mortalities occurred within the first 24 hours. After observation for three weeks the animals were sacrificed and a histological examination was conducted. Lung edema was observed when formaldehyde was administered via the respiratory tract. Animals given formaldehyde subcutaneously, developed liver necrosis.

In a more recent study, Tsuchiya et al.(1975) determined the LD50 oral dosage in male Wistar rats to be 600-700 mg/kg. They observed some

Table 38. Acute Toxicity of Formaldehyde,
Hexamethylenetetramine and Trioxane

Compound	Subject	Number of Animals	Route	LD50	Dosage	Response	Reference
Formaldehyde	Mouse	72	s.c.	300 mg/kg	150-460 mg/kg	Most mortalities occurred within 24 hours	Skog, 1950
"	Rat	64	s.c.	420 mg/kg	300-640 mg/kg	Most mortalities occurred within 24 hours	Skog, 1950
"	Rabbit		s.c.	240 mg/kg			McGuigan, 1914
"	Rat		oral	800 mg/kg (730-870)			Smyth . et al., 1941
"	Rat		oral	100-200 mg/kg			Fassett, 1963
"	Rat-Wistar male	400	oral	600-700 mg/kg		Most mortalities occurred within 24 hours	Tsuchiya et al., 1975
"	Mouse		i.p.	16 mg/kg			Toxic Substances List, 1974
"	Guinea pig		p.c.	260 mg/kg (220-300)			Smyth et al., 1941
"	Rat		intra-vesical	5% formalin		Mortalities occurred in 3 to 5 days	Rankin, 1974
"	Rat	72	Inhal.	1 mg/1. air/ .5 hrs	0.6-1.7 mg/ 1. air	Mortality periods up to 15 days	Skog, 1950
"	Cat		Inhal.	820 mg/m^3/ 8 hrs (LCLo)			Skog, 1950
Hexamethylene-tetramine	Mice		oral	512 mg/kg (LDLo)			Chemical Biological Coordination Center, 1957
"	Rat		i.v.	9200 mg/kg			Toxic Substance List, 1975
Trixane	Rat		oral	800 mg/kg			Frear, 1969

differences in sensitivity in animals of different body weight.

Hexamethylenetetramine is less toxic than formaldehyde. Reported acute toxicity LD50 values for this compound are 512 mg/kg for mice (oral) (Chemical Biological Coordination Center, 1957), and 9200 mg/kg for rats (intravenous) (Toxic Substances List, 1975). The only study found on trioxane reported an LD50 of 800 mg/kg of body weight in rats (Frear, 1969).

2. Subacute/Chronic Toxicity

a. Formaldehyde

The presence of formaldehyde in cigarette smoke, photochemical smog and industrial sources has prompted several chronic exposure studies to determine the effect of formaldehyde on animals. These effects are summarized in Table 39. In a study by Coon _et_ _al_. (1970), rats, guinea pigs, rabbits, monkeys and dogs were continuously exposed to 4.6 ± 0.4 mg/m^3 of formaldehyde for 90 days. Only one death occurred, a rat, all the other animals appeared healthy. Hematologic values were normal, however, some interstitial inflammation occurred in the lungs of all species.

Other long term experiments suggest definite non-physiological changes during continuous prolonged exposure. Fel'dman and Bonashevskaya (1971) report that rats exposed to 0.035 mg/m^3 formaldehyde developed slight variations in vitamin C metabolism. Continual exposure of rats to 1 and 3 mg/m^3 formaldehyde for a period of 3 months produced changes in neurons, receptor synaptic apparatus of dendrites and a proliferative reaction of the perineural glia in nucleii of the cerebral amygdaloid complex (Bonashevskaya, 1973).

Thus, it appears that exposure to concentrations below 1 mg/m^3 of formaldehyde can result in biochemical and tissue changes in animals even though no outward signs of illness are apparent.

Table 39. Chronic Toxicity of Formaldehyde and Hexamethylenetetramine

Compound	Subject	Number of Animals	Route	Concentration	Duration	Daily Intake (g/kg/day)	Response	Reference
Hexamethylene-tetramine	Mouse CTM	50 M; 50 F	oral	0.5	60 weeks	1.25	No apparent effects	Della Porta, 1968
"	Mouse CTM	96 M; 102F	oral	1.0	60 weeks	2.5	No apparent effects	"
"	Mouse CTM	29 M; 50 F	oral	5.0	30 weeks	12.5	Slight growth rate and survival rate reduction	"
"	Mouse SWK	29 M; 27 F	oral	1.0	60 weeks	2.5	Slight growth rate reduction	"
"	Mouse C3Hf	49 M; 44 F	oral	1.0	60 weeks	2.5	No apparent effects	"
"	Rat-Wistar	48 M; 48 F	oral	1.0	104 weeks	2.0-1.5 M 2.5-2.0 F	No apparent effects	"
"	Rat Wistar	12 M; 12 F	oral	5.0	104 weeks		No apparent effects	"
"	Rat	15 M; 15 F	oral	.4 g/1 ml	6 weeks		Yellow coloration of the fur	Brendel, 1964
"	Rat Wistar	16 M; 16 F	oral		lifetime	100 mg/kg	No adverse effects	Natvig, *et al*., 1971
"	Mouse CTM	39 M; 44 F	s.c.	30% W/V	5 Alternate days starting at 10 days of age	25 g/kg total	No apparent effects	Della Porta, 1968
"	Rat Wistar	20 M; 20 F	s.c.	30% W/V	5 alternate days starting at 10 days of age	25 g/kg total	No apparent effects	"
"	Dog, beagle	9 pregnant female			56 days	15 mg/kg/day	No adverse effects on female or pups	Hurni and Ohder, 1973
"	Dog, beagle	10 pregnant females			56 days	31 mg/kg/day	"	"
Formaldehyde	Rats albino	25		3 mg/m^3	3 months		Proliferation of lymphohistiocytic elements in interalveolor walls, Hyperemia	Fel'dman and Bonashevskaya, 1971

Table 39. (Continued)

Compound	Subject	Number of Animals	Route	Concentration	Duration	Daily Intake (g/kg/day)	Response	Reference
Formaldehyde	Rats albino male	25		1 mg/m^3	3 months		Proliferation of lymphohistiocytic elements in interalveolar walls, hyperemia	Fel'dman and Bonashevskaya, 1971
"	"	25		.035 mg/m^3	3 months		Slight variation in Vitamin C metabolism	"
"	"	25		.012 mg/m^3	3 months		No detectable effects	"
"	Rat	15	inhal.	4.6±0.4 mg/m^3	90 day continuous		1 death interstitial inflammatory changes in lungs	Coon et al., 1970
"	Guinea Pig	15	inhal	"	"		No deaths interstitial inflammatory changes in lungs	"
"	Rabbit	3	inhal.	"	"		"	"
"	Dog	3	inhal.	"	"		"	"
"	Monkey	3	inhal.	"	"		"	"
Metaldehyde*	Rat - SPF Wistar	100 M:100F	oral	200 ppm	lifetime			Verschuuren et al., 1975
"	"	100 M:100 F	oral	1000 ppm	lifetime		some posterior paralysis impaired reproductive performance	"
"	"	100 M:100 F	oral	5000 ppm	lifetime		Increase mortality; increase liver weight; posterior paralysis; impaired reproductive performance	"

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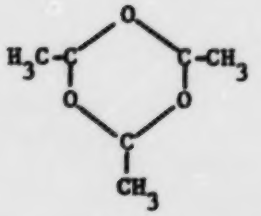
* No references were found for chromic studies of trioxane; Metaldehyde studies were included in the absence of those for trioxane

b. Hexamethylenetetramine and Trioxane

Watanabe and Sugimoto (1955) reported that hexamethylenetetramine caused tumors in rats when subcutaneously injected with aqueous-formic acid solutions. This report caused concern among world health organizations over the danger from the use of hexamethylenetetramine as a food preservative and a urinary antiseptic. Since Watanabe's study several other investigators have evaluated the effects of hexamethylenetetramine over long exposure periods. Della Porta (1968) conducted a well controlled long term (lifetime) oral feeding study in mice and rats. They found no adverse effects on the growth or survival for 0.5 and 1% solution. In 5% solutions some minor growth rate retardation was observed as well as a small decrease in lifespan. Brendel (1964) observed no adverse growth, behavior, mortality or histopathological effects in albino rats fed 200-400 mg hexamethylenetetramine daily for one year. They did, however, observe a yellow coloration of the fur. This coloration is probably due to the reaction between formaldehyde and kynurenine (Kewitz and Welsh, 1966).

In a more recent study by Natvig et al. (1971) no effects on rats were observed from daily ingestion of 100 mg/kg body weight. Lifespan, mean body weights, relative organ weight, muscular activity and palatability of food containing hexamethylenetetramine were observed.

No chronic studies on trioxane were encountered during this survey. A well controlled detailed study on metaldehyde was conducted by Verschuuren et al., 1975. Metaldehyde is the cyclic trimer of acetaldehyde having the following structure



This compound is thus a higher analog of trioxane. Four groups of 25 each male and female SPF Wistar rats were fed 0, 200, 1000 and 5000 ppm metaldehyde in their diet. The rats developed posterior paralysis due to transverse lesion of the spinal cords in doses greater than 1000 ppm. This effect was more pronounced in pregnant females due to the extra strain on the spine. The structural similarity between trioxane and metaldehyde warrants investigation into the long term effects of exposure to trioxane.

3. Sensitization Studies

Sensitization to formaldehyde was examined by Ishikawa (1957), Dueva (1974), Maurer et al. (1975) and Ostapovich (1975). Ishikawa (1957) employed 10 daily subcutaneous injections of formaldehyde to sensitize guinea pigs. Skin sensitivity was tested with dermally applied formaldehyde. An initial period of hyposensitivity was observed on the third through the fifth day after the sensitizing procedures. This period was followed by hypersensitivity to the formaldehyde. Dueva (1974) also studied the effect of tolerance and suppression of sensitization to formaldehyde in guinea pigs. These animals were given single injections into the heart followed by 20 epicutaneous applications of 4% formaldehyde solution 8-14 days later. The optimal tolerance was observed after intracardiac injection of 1000 μg. Doses less than 1000 μg caused partial suppression of contact sensitivity. Higher doses lead to hypersensitivity. The narrow range of doses of formaldehyde producing opposing effects was attributed to its high toxicity and relatively weak allergenic activity.

Maurer et al. (1975) reported that formalin produced distinct reactions upon intradermal challenge after sensitization. Only very weak reactions occur when applied epidermally under occlusion.

Ostapovich (1975) studied the relation of the development of allergic and toxic effects in guinea pigs and albino rats. He suggests that formaldehyde is able to sensitize the body at concentrations of 2 to 7 mg/m^3 during continual exposure. The sensitizing effect may fluctuate during conditions of intermittent inhalation corresponding to the regime used.

4. Teratogenicity and Mutagenicity

Teratogenicity and mutagenicity of oral and inhaled doses of formaldehyde or hexamethylenetetramine in mammals have been studied. These studies are summarized in Table 40. In these cases, effects upon the mother, the pregnancy or the placenta were not observed. Hurni and Ohder (1973) observed beagle pups whose mothers were fed formaldehyde or hexamethylenetetramine beginning on the fourth day after mating and continuing to the 56th day after mating, just prior to delivery of the pups. Of 212 pups observed none showed any effects such as structural or skeletal malformations. Pups from mothers receiving high doses of hexamethylenetetramine (1250 ppm in feed) showed increased perinatal mortality and growth retardation. Other groups receiving formaldehyde (125 ppm or 375 ppm in food) or low doses of hexamethylenetetramine (600 ppm) were essentially normal. Some of the pups were returned to the breeding colony and as of the time of report, their offspring had shown no abnormalities in number or structure.

Table 40. Teratogenic and Mutagenic Effects of Formaldehyde and Hexamethylenetetramine

Compound	Species	Number of Animals	Route	Dosage Rate	Dosage Period	Number of Offspring	Malformations	Remarks	Reference
Hexamethyl-enetetramine	Rat-Wistar	6 M; 6 F	Oral	1% in water daily	2 wks before mating through pregnancy and lactation weaning to 20 wks	124	None at birth	Body weight was lower thar controls until 9-13 weeks old	Della Porta, 1970
	Rat-Wistar	24	oral	1% in water daily	"				
"	Rat-Wistar F$_1$		oral	"	40 weeks			No evidence of gross or histopathogical changes or carcinogenicity	"
	Rat-Wistar F$_2$		"	"	40 weeks				
	Rat-Wistar F$_3$		"	"	20 weeks				
"	Dogs	8 bitches	oral	15 mg/kg/day	56 days	50 (2 dead)		No structural or other malformation	Hurni and Ohder, 1973
		9 bitches	oral	31 mg/kg/day	56 days	56 (10 dead)		"	"
Formaldehyde	Rat	male	inhal	1 mg/m^3	10 days			No changes in testes	Gofmekler and Bonashevskaya, 1969
"	Rat	female	inhal	1 mg/m^3				No structural deformaties or inhibition of organ development; did cause various histological changes	"
"	Rat	female	inhal	0.012 mg/m^3				No gross or histopathological effects observed	"
"	Dogs-beagle	10 female	oral	3.1 mg/kg/day	56 days	54 (4 dead)		No physiological or skeletal abnormalities	Hurni and Ohder, 1973
		9 female	oral	9.4 mg/kg/day	56 days	64 (no deaths)		"	"

Gofmekler and Bonashevskaya (1969) showed inconclusively that continuous inhalation of 1 mg/m^3 of formaldehyde by pregnant rats, for an unreported time period, led to histological changes in the liver, bile duct and kidneys of offspring. No correlation with physiological impairment of these organs was attempted.

Studies to date have failed to indicate any gross teratogenic or mutagenic response to either formaldehyde or hexamethylenetetramine. It is expected that some histogical changes of unknown significance may occur to the embryo exposed to formaldehyde in utero.

5. Carcinogenicity in Mammals

Since formaldehyde is a known alkylating agent, its carcinogenic potential and that of hexamethylenetetramine have been the subject of several studies. A summary of the data from these studies is given in Table 41. The implications of this data are discussed in this section.

A preliminary report of positive carcinogenic response to formaldehyde was made by Watanabe et al. in 1954. These authors observed sarcomas at the site of injection in two of ten rats given weekly subcutaneous doses of formaldehyde over 15 months (total dose 260 mg/rat). There were also tumors of the liver and omentum in two other rats. However, the group under study was very small and the authors do not mention any controls. A second report by Watanabe and Sugimura (1955) describes the induction of tumors at the site of subcutaneous injection of hexamethylenetetramine in eight out of fourteen animals surviving the three month dosage period (injections of

Table 41. Carcinogenicity Studies Involving Formaldehyde and Hexamethylenetetramine

Compound	Subject	No. of Animals		Route	Concentration	Duration	Daily Intake (g/kg/day)	Animals without Tumors Control			Animals without Tumors Treated			Response	Reference
		Control	Test					Ser. No.	%	Age(wks)	Ser. No.	%	Age(wks)		
Hexamethylene-tetramine	Mouse CTM	98 M 99 F	50 M 48 F	oral	0.5%	60 wks	1.25	M 43 F 32	44 32	79±6 87±6	M 23 F 12	46 25	80±8 87±12		Della Porta *et al*. 1968
"	"	98 M 99 F	94 M 102 F	oral	1.0%	60 wks	2.5		44 32		M 37 F 25	39 24	83±8 88±9		"
"	"	96 M 99 F	27 M 48 F	oral	5.0%	30 wks	12.5		44 32		M 19 F 12	70 25	64±14 71±20		
"	Mouse SWR	43 M 27 F	28 M 24 F	oral	1.0%	60 wks	2.5	M 21 F 9	49 33	59±9 90±10	M 16 F 12	57 50	78±13 91±14		
"	Mouse C3Hf	30 M 62 F	49 M 40 F	oral	1.0%	60 weeks	2.5	M 9 F 16	30 26	108±18 117±10	M 27 F 20	55 50	95±10 103±10		
"	Mouse CTM		38 M 40 F	s.c.	5 g/kg x 5	alternate days	25 g/kg total				M 19 F 15	50 37	91±6 83±10		
"	Rat Wistar	47 M 48 F	48 M 48 F	oral	1.0%	104 wks	2.0-15 M 2.5-2.0 F	M 8 F 11	17 23	114±31 122±14	M 12 F 21	25 44	123±13 113±10		
"	Rat Wistar	49 M 48 F	6 M 6 F	oral	5.0%	104 wks		M 8 F 11	17 23	114±31 122±14	M 2 F 3	33 43	144±5 104±0		
"	Rat Wistar		18 M 19 F	s.c.	5 g/kg x 5	alternate days	25 g/kg total				M 8 F 11	44 58	100±12 96±10		
"	Rats		20	s.c.	1 or 2 ml of 9 or 23% + 0.5 ml .1% formic acid	3 months					6			6 died of unknown illness 8 of remaining 14 had tumors at injection site	Watanabe *et al*. 1955
Formaldehyde	Mice C3H	59	60	inhal	0.5 mg/l	105 x 1 hr.					59				Della Porta *et al*., 1968
"		59	60	inhal	0.1 mg/l	105 x 1 hr.					59				"
		59	42	inhal	0.2 mg/l	11 x 1 hr.					42			all died after 11 days of exposure	Horton *et al*., 1963
"	Rats		10	s.c.	1 x/wk	15 wks	total 260-325 mg				8			2 of 10 showed sarcomas at injection site 81 & 93 wks.	Watanabe *et al*., 1954

1.0 or 2.0 ml of 23% hexamethylenetetramine twice weekly). The animals were simultaneously made acidic by subcutaneous injection of 0.5 ml of 0.1% formic acid. Again, this study was not controlled, although both were lifetime studies.

A negative report of carcinogenicity was made by Horton et al. (1963). Formaldehyde was administered by intermittent inhalation (1 hour x 3 days for 35 or 64 weeks) to C3H mice. These animals showed no pulmonary tumors at 64 weeks at levels of 0.05, 0.10 and 0.20 mg/liter. Levels of 0.20 mg/liter were not tolerated well and many animals died after the sixth hour of exposure. Respiratory tissues were observed to be undergoing histological changes "similar to precancerous lesions observed in cigarette smokers." Unfortunately, observation was not carried out for the lifetime of the mice and other organs were not examined for histopathology, thereby limiting the value of this study.

Della Porta et al. (1968) have reported a large and well controlled study on the carcinogenicity of hexamethylenetetramine. These lifetime studies were conducted on one strain of rat and 3 strains of mice (one outbred and two inbred) given hexamethylenetetramine in drinking water. The dosing period was from 30-60 weeks in mice and 104 weeks in rats, using doses of hexamethylenetetramine which caused no toxicity and minimal depression in weight gain. No evidence of carcinogenicity was found, a conclusion which agrees with Brendel's 1964 study on rats given 400 mg/day hexamethylenetetramine orally for 1 year.

The only data purporting to demonstrate that formaldehyde or hexamethylenetetramine are carcinogenic are Watanabe's uncontrolled studies in rats dosed repeatedly with high concentrations of these substances by subcutaneous injection. The doses and injection volumes used caused irritation and scarring at the injection site. It is well known that repeated, nonspecific irritation of the skin and many other organs can lead to the appearance of tumors. The lack of reported results from control animals and the fact that the route of administration is not related to common environmental modes of exposure, reduces the significance of Watanabe's studies. The "negative" result data is also difficult to interpret. Only two rodent species have been tested and in each case the tests were conducted at less than maximally tolerated levels and/or for less than the lifetime of the animals.

It should be noted that while the animal data in support of carcinogenic activity of formaldehyde is weak, formaldehyde has been shown to be a mutagen in a number of systems. One of these systems is currently used as an indicator of carcinogenic potential. This indicator is a special strain of *E. coli* B/r. which lacks repair capacity (pol A^-). Rosenkranz (1972) has described the interaction of formaldehyde with both the Pol A^+ and Pol A^- strains as "characteristic of known carcinogens." That is, formaldehyde showed a "preferential inhibition" of growth of the Pol A^- strain.

These bacterial tester strains currently in use for the prediction of potential hazard have shown a reasonably good correlation between mutagenicity in the bacterial system and carcinogenicity *in vivo*. Where data is sufficient and reliable, many known carcinogens have been shown to be mutagens and with some notable exceptions vice versa.

In summary, it appears that no conclusion is possible other than it is unlikely that formaldehyde is a strong carcinogen in mammals. However, the results of the mutagenicity testings of Rosenkranz and others indicate that further tests should be conducted. Since human exposure to formaldehyde is likely to be by inhalation, a possible test system would be the strain A mouse. This mouse has been used for years to test the activity of pulmonary carcinogens because of its high susceptibility to such agents.

6. Behavior - Symptomology

With exposure to sublethal concentrations of formaldehyde in air, animals exhibit coughing, sneezing, eye irritation, salivation, slowed respiration and loss of appetite (Sterner, 1963). Lethal concentrations cause symptoms of severe pulmonary involvement followed by death.

7. Possible Synergistic Effects

Synergistic actions on the respiratory functions of guinea pigs have been found for a combination of formaldehyde and inert sodium chloride aerosols (Amdur, 1960). The guinea pigs showed a response to the combined exposure that was greater than that for formaldehyde alone. No response was found for inhalation of the aerosol without the formaldehyde.

There is a definite need for additional well controlled synergistic studies of formaldehyde and other components of photochemical smog and cigarettes especially CO, SO_2, H_2SO_4 aerosol, HCl and NO_x.

8. Animal Nutrition

When ruminants are fed diets high in soluble protein or low in readily available energy, deamination of dietary proteins by rumen microorganisms becomes of great importance. Deamination of proteins can result in a large proportion of potentially useful nitrogen being lost from the rumen as ammonia. Formaldehyde has been used to protect dietary protein from microbial proteolysis in the rumen in an effort to increase the efficiency of utilization of amino acids for wool and body growth in sheep and other ruminants (Ferguson _et_ _al_., 1967; Ferguson, 1970; Faichney 1970).

Casein and protein-rich meals were treated with formalin by Ferguson _et_ _al_. (1967) to form a protective polymeric coating composed of methylene cross bridges between protein chains. Sheep fed the supplement increased both rate of wool growth and rate of live-weight gain. Barry (Hemsley _et_ _al_., 1973) conducted an experiment in which pregnant ewes were fed diets containing formaldehyde-treated casein. Results indicated that the response depended on the plane of nutrition. When formaldehyde treated casein was fed to ewes on a lower plane of nutrition no effect on wool growth response was observed, but the birth and growth rates of their lambs were greater than for those lambs born to the control ewes.

Formaldehyde-treated casein which contained 0.5 - 1.5% bound formaldehyde increased wool growth rate and fiber diameter substantially when included in the diet of sheep (Hemsley _et_ _al_., 1973). The greatest wool growth response was obtained with casein preparations containing about 1% bound formaldehyde, regardless of the treatment procedure. The preparations that were most effective corresponded to treatments that afforded good protection in vitro without producing an appreciable reduction in digestibility. Ineffective casein preparations were either incompletely protected in the rumen or had a lowered digestibility.

There may be little advantage in completely protecting protein from microbial degradation in the rumen because digestibility in the intestines may be reduced. The results of formaldehyde-treated casein cannot be applied directly to the formaldehyde treatment of protein-rich feedstuffs normally fed to ruminants. Such materials consist of many compounds besides protein which could react with formaldehyde. The proteins may also vary in their susceptibility to rumenal degradation and may have biological values which are appreciably different from that of casein. Limited information indicates that the formaldehyde-treatment of various proteins may produce different results from those obtained with casein.

Sheep fed formaldehyde-treated (2.5% formalin) linseed meal and meatmeal showed differences in nitrogen retention but no significant differences in wool growth or live-weight gain (Rattray and Joyce, 1970). Cottonseed meal treated with varying amounts of formaldehyde by a low-volume procedure showed less decline in digestibility than that observed with casein (Hemsley et al., 1973; Langlands, 1971). Also, formaldehyde treatment did not enhance the nutritional value of cottonseed meal for wool growth (Langlands, 1971). Using more than 2 ml of formalin (40%) per 100 g of soybean protein reduces growth in ruminants, presumably by reducing the digestibility of the protein (Schmidt et al., 1973). By contrast, formaldehyde treatment of artificially dried clover (Hemsley et al., 1973) significantly increased both protein digestion in the intestines and wool production in sheep.

The use of formaldehyde-treated protein in ruminant nutrition does not produce an accumulation of formaldehyde in tissues or milk (Mills et al., 1972). Formaldehyde is effectively metabolized to CO_2 and cellular constituents. The mean retention time in the rumen and hind gut was decreased when a formaldehyde treated concentrate diet was fed to sheep, but increased in the abomasum and small intestine (Faichney, 1975).

It is apparent that a decrease in the digestion coefficient of nitrogen and an increase in nitrogen retention for ruminants occurs when animals are fed formaldehyde-treated silage, however the specification for treatment levels of formaldehyde necessary for maximum nitrogen retention needs to be defined more clearly. Hexamethylenetetramine will chemically bind to soybean proteins as indicated by in vitro ammonia release (Schmidt et al., 1973). since it is safe and easy to handle, its potential for use in ruminant nutrition warrants further investigation.

E. Toxicity - Birds

Limited information is available on specific bird-formaldehyde toxicity studies. Hartmen et al. (1954) conducted experiments with 2-3 week old pelicans (*Pelecanus occidentalis*). In this study, histological and cytological changes in the adrenal gland due to formaldehyde induced stress were monitored. Six birds weighing 1250-1700 g were injected subcutaneously with 5 cm^3 of 3.6% formaldehyde and sacrificed 2 to 72 hours later. There was little evidence of abnormal mitosis and degeneration of the adrenal gland was moderate after 72 hours.

A study of the penetrability of formaldehyde into chicken and turkey hatching eggs shows that low levels of formaldehyde were found in the shell membrane homogenates after 20 minutes of fumigation at a concentration of 1.2 ml/ft^3 formalin (Williams and Siegal, 1969). Very low levels were found in the albumen indicating that formaldehyde penetrated the shell only slightly.

In a follow up study, the hatchability of eggs after treatment for 20 minutes at 1X, 3X and 5X the 1.2 ml formalin per ft^3, showed no significant difference between fumigated and unfumigated eggs. This suggests that relatively high levels of fumigant may not excessively depress hatchability (Williams and Gordon, 1970).

F. Toxicity - Lower Animals and Microorganisms

The discussions of the toxic action of formaldehyde on lower animals and microorganisms are combined in this section in order to present a more concise view of the subject. The combination of these two sections was considered expedient for two reasons.

(1) The majority of the toxicity data on lower animals is the result of therapeutic treatment to kill parasites, fungi and bacteria.

(2) The studies on formaldehyde mutagenicity have been conducted using Drosophila and microorganisms.

1. Fish

The use of formalin as a chemotherapeutant for control of fungus on fish eggs and ectoparasites on fish is a widely accepted and successful technique. However, unless certain criteria are met formalin may exert acute pathological effects. The acute toxicity of formalin to fish was summarized by Schnick (1973). This summary is presented in Table 42 . The Table is arranged in phylogenetic order using common names of the fishes. Due to insufficient data on pH, hardness, and composition, no column for water chemistry was included. Discrepancies in the data can be attributed to the physical condition of the fish, lack of a significant sample, inadequate numbers of fish, different strains of resistant or tolerant species or different water temperatures.

Analysis of toxicity levels indicates that a wide range of tolerances exist for different species. In 24-hour LC 50's it appears that striped bass are the most sensitive (LC50 - 15 to 35 µl/1) and salmonids and centrarchids are the least sensitive with LC50 ranges from 135 to 325 µl/1. In cases where experiments were similar except for temperature, formalin was more toxic at higher temperatures.

When fish are exposed to a toxic dose of formalin, they react variously by surfacing, snapping jaws, going off feed, and becoming stupefied (Holland et al., 1960). Physiologically, they first respond to formalin toxicity by changing color, decreasing gill function, changing blood chemistry, and losing equilibrium (Wedemeyer, 1971; Smith and Piper, 1972; Western Fish Disease Laboratory, 1971a, 1971b; and Division of Fish Hatcheries, 1969b). Some species of fish exhibit a particular sensitivity to formalin which cannot be explained in terms of environmental factors or physical condition of the fish. Particular species or populations appear stressed as in the case with certain ictalurids, salmonids, gizzard shad, and striped bass.

TABLE 42. Fish Toxicity to Formalin (Schnick, 1973)

Species	Toxic concentration	Exposure	Dose (μl/l)	Temp. (°C)	Size	Percent formalin	Reference
Trouts							
Salmon sp.	Nontoxic	1 hr	500 (1:2,000)	8.3	Fingerlings	37	Fish and Burrows,1940
	Nontoxic	30 min	1,000 (1:1,000)	7.2	Fingerlings	37	Fish and Burrows,1940
	Nontoxic	2 hr	500 (1:2,000)	7.8	Fingerlings	37	Fish and Burrows,1940
	Nontoxic	2 hr	250 (1:4,000)	5.3	Fingerlings	37	Fish and Burrows,1940
	Nontoxic	3 hr	167 (1:6,000)	8.6	Fingerlings	37	Fish and Burrows,1940
	Toxic	1 hr	1,000 (1:1,000)	7.2	Fingerlings	37	Fish and Burrows,1940
	Toxic	4 hr	500 (1:2,000)	7.8	Fingerlings	37	Fish and Burrows,1940
	Toxic	4 hr	333 (1:3,000)	9.7	Fingerlings	37	Fish and Burrows,1940
Chinook salmon	LC50	< 51 hr	135 (50 ppm-100%)	13.6	67 mm	37	Holland *et al.*, 1960
	LC50	> 72 hr	76 (28.2 ppm-100%)	13.6	67 mm	37	Holland *et al.*,1960
	LC100	< 70 hr	135 (50 ppm-100%)	13.6	67 mm	37	Holland *et al.*,1960
	LC100	> 72 hr	76 (28.2 ppm-100%)	13.6	67 mm	37	Holland *et al.*.1960
Rainbow trout	LC50	< 23.8 hr	270 (100 ppm-100%)	13.6	80 mm	37	Holland *et al.*, 1960
	LC50	24 hr	207 (ppm)	12	38.46 mm	37	Willford,1967
	LC50	24 hr	203.5 (76 ppm-100%)	18	Under yearling	37	Alabaster, 1969
	LC50	< 45 hr	152 (56.3 ppm-100%)	13.6	80 mm	37	Holland *et al.*, 1960
	LC50	48 hr	168 (ppm)	12	38-46 mm	37	Willford,1967
	LC50	48 hr	135 (50 ppm-100%)	18	Under yearling	37	Alabaster, 1969
	LC100	< 26 hr	270 (100 ppm-100%)	13.6	80 mm	37	Holland *et al.*, 1960
	LC100	< 70 hr	152 (56.3 ppm-100%)	13.6	80 mm	37	Holland *et al.*, 1960
Brown trout	LC50	24 hr	325 (ppm)	12	43-48 mm	37	Willford, 1967
	LC50	24 hr	205.5 (76 ppm-100%)	18		37	Alabaster, 1969
	LC50	48 hr	185 (ppm)	12	43-48 mm	37	Willford,1967
	LC50	48 hr	135 (50 ppm-100%)	18		37	Alabaster, 1969
Brook trout	LC50	24 hr	196 (ppm)	12	38-40 mm	37	Willford,1967
	LC50	48 hr	157 (ppm)	12	38-40 mm	37	Willford, 1967

TABLE 42 (Continued)

Species	Toxic concentration	Exposure	Dose (μl/l)	Temp. (° C)	Size	Percent formalin	Reference
Lake trout	LC50	24 hr	220 (ppm)	12	102 mm	37	**Willford, 1967**
	LC50	48 hr	167 (ppm)	12	102 mm	37	**Willford, 1967**
Trout	Troubled (word of author)	1.5 hr	500 (1:2,000)	7	Fry	37	**Hewitt, 1940**
Characins							
Glowlight tetra	LC	72 hr	100 (10 c cs of 1% v/v per 1)	--	--	37	**Rankin, 1952**
Minnows and carps							
Common moderlieschen (Verkhova)	LC100	51 days	54 (20 mg/1-100%)	--	Fry	37	**Nazarenko, 1960**
Veiltail goldfish	LC	72 hr	100	--	Fry	37	**Rankin, 1952**
Goldfish	LC0	1 hr	200 (ppm)	--	25-182 mm	37	**Estes, 1957**
	LC0	72 hr	52 (ppm)	--	25-182 mm	37	**Estes, 1957**
	LC50	1 hr	1,000 (ppm)	18	.186 g(average)	37	**Peterson, 1971**
	LC50	24 hr	100 (ppm)	--	25-182 mm	37	**Estes, 1957**
	LC50	24 hr	118 (ppm)	18	.186 g (average)	37	**Peterson, 1971**
	LC50	48 hr	77 (ppm)	18	.186 g (average)	37	**Peterson, 1971**
	LC50	72 hr	73 (ppm)	18	.186 g (average)	37	**Peterson, 1971**
	LC50	96 hr	73 (ppm)	18	.186 g (average)	37	**Peterson, 1971**
	LC60	30 min	5,000 (ppm)	--	Newly hatched fry	37	**Estes, 1957**
Carp	LC0	48 hr	100 (ppm)	23	30-200 g	40	**Lahav and Sarig, 1972**
	LC	3 hr	250 (ppm)	15-22	--	formalin	**Sarig, 1971**
	LC	8 hr	100 (ppm)	15-22	--	formalin	**Sarig, 1971**
	LC50	1 hr	2,840	12	25-50.8 mm	37	**Marking *et al.*, 1972**
	LC50	3 hr	880	12	25-50.8 mm	37	**Marking *et al.*, 1972**
	LC50	6 hr	640	12	25-50.8 mm	37	**Marking *et al.*, 1972**
	LC50	24 hr	262	12	25-50.8 mm	37	**Marking *et al.*, 1972**
	LC50	24 hr	100 (ppm)	23	.3-10 g	40	**Lahav and Sarig, 1972**
	LC50	72 hr	70+ (ppm)	--	50 mm	38	**Helms, 1967**
	LC50	96 hr	71 (ppm)	12	25-50.8 mm	37	**Marking *et al.*, 1972**

TABLE 42 (Continued)

Species	Toxic Concentration	Exposure (ul/1)	Dose (°C)	Temp.	Size	Percent	Reference
Carp	LC100	.2 hr	500 (ppm)	18-23	50 g	40	Lahav and Sarig, 1972
	LC100	10 hr	200 (ppm)	18-23	50 g	40	Lahav and Sarig, 1972
	LC100	24 hr	140 (ppm)	23	.3-10 g	40	Lahav and Sarig, 1972
	LC100	24 hr	140 (ppm)	23	30-200 g	40	Lahav and Sarig, 1972
Golden Shiner	LC0	2 hr	125 (ppm)	21.7-26	76 mm	40	Lewis and Lewis, 1963
	LC0	18 hr	50 (ppm)	21.7-26	76 mm	40	Lewis and Lewis, 1963
	LC50	65 min	250 (ppm)	21.7-26	76 mm	40	Lewis and Lewis, 1963
	LC50	24 hr	87 (ppm)	--	76-102 mm	38	Helms, 1967
	LC50	48 hr	67 (ppm)	--	76-102 mm	38	Helms, 1967
	LC50	72 hr	62 (ppm)	--	76-102 mm	38	Helms, 1967
	LC100	72 hr	120 (ppm)	21.7-26	76 mm	40	Lewis and Lewis, 1963
Emerald Shiner Spotfin shiner	LC1	>120 hr	135 (50ppm-100%)	18	--	37	Van Horn *et al.*, 1950 McKee and Wolf, 1971
Fathead Minnow	LC50	1 hr	749 (ppm)	18	.21 g (average)	37	Peterson, 1971
	LC50	24 hr	66 (ppm)	18	.21 g (average)	37	Peterson, 1971
	LC50	48 hr	44 (ppm)	18	.21 g (average)	37	Peterson, 1971
	LC50	72 hr	41 (ppm)	18	.21 g (average)	37	Peterson, 1971
	LC50	96 hr	41 (ppm)	18	.21 g (average)	37	Peterson, 1971
Freshwater catfishes							
Black bullhead	LC50	24 hr	70+(ppm)	--	51 mm	38	Helms, 1967
	LC50	48 hr	49 (ppm)	--	51 mm	38	Helms, 1967
	LC50	72 hr	45 (ppm)	--	51 mm	38	Helms, 1967
Channel catfish	LC0	1 hr	316 (ppm)	25	51-76 mm	37	Clemens and Sneed, 1958, 1959
	LC0	25-96 hr	50 (ppm)	25	51-76 mm	37	Clemens and Sneed, 1958, 1959
	LC50	1 hr	500 (ppm)	25	51-76 mm	37	Clemens and Sneed, 1958, 1959

TABLE 42. (Continued)

Species	Toxic concentration	Exposure	Dose (ul/1)	Temp. (°C)	Size	Percent formalin	Reference
Channel catfish	LC50	1 hr	780 (ppm)	12	25-50.8mm	37	Marking et al., 1972
	LC50	2 hr	263 (ppm)	25	51-76 mm	37	Clemens and Sneed, 1958, 1959
	LC50	3 hr	460 (ppm)	12	25-50.8mm	37	Marking et al., 1972
	LC50	4 hr	165 (ppm)	25	51-76 mm	37	Clemens and Sneed, 1958, 1959
	LC50	6 hr	330	12	25-50.8 mm	37	Marking et al., 1972
	LC50	8 hr	138 (ppm)	25	51-76 mm	37	Clemens and Sneed, 1958, 1959
	LC50	24 hr	145	12	25-50.8 mm	37	Marking et al., 1972
	LC50	24 hr	137 (ppm)	17	53-56 mm	37	Willford, 1967
	LC50	25 hr	87 (ppm)	25	51-76 mm	37	Clemens and Sneed, 1958, 1959
	LC50	48 hr	96 (ppm)	17	53-56 mm	37	Willford, 1967
	LC50	48-96 hr	69 (ppm)	25	51-76 mm	37	Clemens and Sneed, 1958, 1959
	LC50	96 hr	69 (mg/1)	25	51-76 mm	37	Reichenbach-Klinke, 1966
	LC50	96 hr	66	12	25-50.8 mm	37	Marking et al., 1972
	LC100	1 hr	> 500 (ppm)	25	51-76 mm	38	Clemens and Sneed, 1958, 1959
	LC100	2 hr	500 (ppm)	25	51-76 mm	38	Clemens and Sneed, 1958, 1953
	LC100	4 hr	316 (ppm)	25	51-76 mm	38	Clemens and Sneed, 1958, 1953
	LC100	8 hr	199 (ppm)	25	51-76 mm	38	Clemens and Sneed, 1958, 1953
	LC100	25-96 hr	126 (ppm)	25	51-76 mm	38	Clemens and Sneed, 1958, 1953.
	LC100	96 hr	126 (mg/1)	25	51-76 mm	38	Reichenbach-Klinke, 1966
Sticklebacks							
Ten-spined sticklebacks	Irritated Stupefied	26 min	1,000-2,000 (0.1-0.4%)	15	25-30 mm	40	Jones, 1947

TABLE 42. (Continued)

Species	Toxic concentration	Exposure	Dose (µl/1)	Temp. (°C)	Size	Percent formalin	Reference
Temperate basses							
Striped bass	LC0	24 hr	10	21	1 week old	37	Hughes, 1969
	LC0	48 hr	10	21	1 week old	37	Hughes, 1969
	LC0	72 hr	10	21	1 week old	37	Hughes, 1969
	LC0	96 hr	5	21	1 week old	37	Hughes, 1969
	LC0	24 hr	30	21	30-52 mm	37	Hughes, 1969
	LC0	48 hr	15	21	30-52 mm	37	Hughes, 1969
	LC0	72 hr	10	21	30-52 mm	37	Hughes, 1969
	LC0	96 hr	5	21	30-52 mm	37	Hughes, 1969
	LC16	24 hr	52 (ppm)	21	60 mm	37	Wellborn, 1969
	LC16	48 hr	20 (ppm)	21	60 mm	37	Wellborn, 1969
	LC16	96 hr	12 (ppm)	21	60 mm	37	Wellborn, 1969
	LC50	24 hr	15 (ppm)	21	1 week old	37	Hughes, 1969
	LC50	48 hr	15 (ppm)	21	1 week old	37	Hughes, 1969
	LC50	72 hr	15 (ppm)	21	1 week old	37	Hughes, 1969
	LC50	96 hr	10 (ppm)	21	1 week old	37	Hughes, 1969
	LC50	24 hr	35 (ppm)	21	30-52 mm	37	Hughes, 1969
	LC50	24 hr	86 (ppm)	21	60 mm	37	Wellborn, 1969; Pimental, 1971
	LC50	48 hr	15 (ppm)	21	30-52 mm	37	Hughes, 1969
	LC50	48 hr	32 (ppm)	21	60 mm	37	Wellborn, 1969
	LC50	72 hr	15 (ppm)	21	30-52 mm	37	Hughes, 1969
	LC50	96 hr	15 (ppm)	21	30-52 mm	37	Hughes, 1969
	LC50	96 hr	18 (ppm)	21	60 mm	37	Wellborn, 1969
	LC100	24 hr	40 (ppm)	21	30-52 mm	37	Hughes, 1969
	LC100	48 hr	25 (ppm)	21	30-52 mm	37	Hughes, 1969
	LC100	72 hr	25 (ppm)	21	30-52 mm	37	Hughes, 1969
	LC100	96 hr	25 (ppm)	21	30-52 mm	37	Hughes, 1969

TABLE 42. (Continued)

Species	Toxic concentration	Exposure	Dose (µl/l)	Temp. (°C)	Size	Percent formalin	Reference
	LC100	24 hr	35	21	1 week old	37	Hughes, 1969
	LC100	48 hr	30	21	1 week old	37	Hughes, 1969
	LC100	72 hr	30	21	1 week old	37	Hughes, 1969
	LC100	96 hr	30	21	1 week old	37	Hughes, 1969
Sunfishes							
Green sunfish	LC50	72 hr	90+(ppm)	--	76 mm	38	Helms, 1967
Bluegill	LC50	30 min	6,010 (ppm)	12	25-50.8 mm	37	Marking, 1970
	LC50	1 hr	3,160 (ppm)	12	25-50.8 mm	37	Marking, 1970
	LC50	1 hr	425	18	.324 g (average)	37	Peterson, 1971
	LC50	3 hr	1,550 (ppm)	12	25-50.8 mm	37	Marking, 1970
	LC50	3 hr	2,300 (ppm)	12	25-50.8 mm	37	Marking *et al.*, 1972
	LC50	6 hr	1,050	12	25-50.8 mm	37	Marking *et al.*, 1972
	LC50	6 hr	1,050 (ppm)	12	25-50.8 mm	37	Marking, 1970
	LC50	24 hr	254 (ppm)	12	25-50.8 mm	37	Marking, 1970
	LC50	24 hr	299	12	25-50.8 mm	37	Marking *et al.*, 1972
	LC50	24 hr	185 (ppm)	12	40-43 mm	37	Willford, 1967
	LC50	24 hr	70 (ppm)	18	.324 g (average)	37	Peterson, 1971
	LC50	48 hr	100+(ppm)	--	76 mm	38	Helms, 1967
	LC50	48 hr	140 (ppm)	12	40-43 mm	37	Willford, 1967
	LC50	48 hr	66 (ppm)	18	.324 g (average)	37	Peterson, 1971
	LC50	72 hr	80 (ppm)	--	76 mm	38	Helms, 1967
	LC50	72 hr	56 (ppm)	18	.324 g (average)	37	Peterson, 1971
	LC50	96 hr	56 (ppm)	18	.324 g (average)	37	Peterson, 1971
	LC50	96 hr	127 (ppm)	12	25-50.8 mm	37	Marking, 1970
	LC50	96 hr	82 (ppm)	12	25-50.8 mm	37	Marking *et al.*, 1972
Smallmouth bass	LC50	24 hr	222	12	25-50.8 mm	37	Marking *et al.*, 1972
	LC50	24 hr	153	12	25-50.8 mm	37	Marking *et al.*, 1972
	LC50	96 hr	136	12	25-50.8 mm	37	Marking *et al.*, 1972
	LC50	96 hr	83.2	12	25-50.8 mm	37	Marking *et al.*, 1972

TABLE 42. (Continued)

Species	Toxic concentration	Exposure	Dose (µl/1)	Temp. (°C)	Size	Percent formalin	Reference
Largemouth bass	LC50	1 hr	422	28	.736 g (average)	37	Peterson, 1971
	LC50	6 hr	1,030	12	25-50.8 mm	37	Marking et al., 1972
	LC50	24 hr	283	12	25-50.8 mm	37	Marking et al., 1972
	LC50	24 hr	135 (ppm)	21	.736 g (average)	37	Peterson, 1971
	LC50	48 hr	83 (ppm)	21	.736 g (average)	37	Peterson, 1971
	LC50	72 hr	56 (ppm)	21	.736 g (average)	37	Peterson, 1971
	LC50	72 hr	100+(ppm)	--	102-127 mm	38	Helms, 1967
	LC50	96 hr	56 (ppm)	21	.736 g (average)	37	Peterson, 1971
	LC50	96 hr	143	12	.736 g (average)	37	Marking et al., 1972
Jacks and pompanos							
Florida pompano	LC50	24 hr	78 (ppm) in 10 ppt**	20-25	25 mm	37	Birdsong and Avault, 1971
	LC50	24 hr	84 (ppm) in 20 ppt	20-25	25 mm	37	Birdsong and Avault, 1971
	LC50	24 hr	78 (ppm) in 30 ppt	20-25	25 mm	37	Birdsong and Avault, 1971
	LC50	48 hr	78 (ppm) in 10 ppt	20-25	25 mm	37	Birdsong and Avault, 1971
	LC50	48 hr	78 (ppm) in 20 ppt	20-25	25 mm	37	Birdsong and Avault, 1971
	LC50	48 hr	73.7 (ppm) in 30 ppt	20-25	25 mm	37	Birdsong and Avault, 1971
	LC50	96 hr	74.9 (ppm) in 10 ppt	20-25	25 mm	37	Birdsong and Avault, 1971
	LC50	96 hr	71.6 (ppm) in 20 ppt	20-25	25 mm	37	Birdsong and Avault, 1971
	LC50	96 hr	69.1 (ppm) in 30 ppt	20-25	25 mm	37	Birdsong and Avault, 1971
Cichlids							
Tilapia sp.	LC0	48 hr	100 (ppm)	23	30 g	40	Lahav and Sarig, 1972
	LC50	24 hr	100 (ppm)	23	.03 g	40	Lahav and Sarig, 1972
	LC50	72 hr	100+(ppm)	—	76 mm	38	Helms, 1967
	LC100	24 hr	140 (ppm)	23	.03 g	40	Lahav and Sarig, 1972
	LC100	24 hr	140 (ppm)	23	30 g	40	Lahav and Sarig, 1972

* 100%-formaldehyde, ** Saline waters.

Most fish can tolerate a standard treatment of 250 μl/1 of formalin for 1 hour but gizzard shad cannot (Peterson et al., 1966). Slightly parasitized channel catfish and black bullhead cannot withstand treatments of 170 μl/1 (Division of Fish Hatcheries, 1966). Although striped bass can tolerate higher concentrations such as 250 μl/1 of formalin for short periods of time (1 hour), they are sensitive to lower concentrations of 15 μl/1 for long periods of time (Wellborn, 1969). The 96-hour LC50's are 10 μl/1 for 1 month old fish (Hughes, 1969). Striped bass fingerlings experienced 15 to 25% mortality 96 hours after exposure to 167 to 333 μl/1 of formalin for 1 hour. No mortality or stress was observed during the treatment or during the following 24 hours. Peterson et al., (1972) reported that Atlantic salmon may become stressed when standard treatments are given too frequently. Rainbow trout sensitivity to formalin applications appears to vary with the particular strain of fish. Some strains are highly sensitive to formaldehyde causing problems in hatcheries where formalin is used to control disease (Smith and Piper, 1973; Rucker et al., 1963; Wood, 1968; Wedemeyer, 1971).

Genetic studies with rainbow trout show that offspring of resistant parents tolerate significantly higher concentrations than offspring of either unselected or susceptible parents. Thus formalin tolerance is apparently a strongly heritable trait (Fish Genetics Laboratory, 1970). The 6-hour LC50 for progeny of resistant parents was 470 μl/1; for progeny of unselected parents, it was 346 μl/1; and for progeny of susceptible parents, it was 283 μl/1.

Physiologically, rainbow trout react differently to formalin than other salmonids. Histological and hematological changes occur which reduce the species ability to maintain osmotic and acid-base balance (Smith and Piper, 1972). In comparative studies of formalin stress, these changes caused greater bilirubinemia in rainbow trout than in Coho salmon. Blood pH and alkaline reserve in rainbow trout were less well regulated than in the Coho. The Coho was also able to maintain several metabolic parameters which rainbow trout were unable to do (Wedemeyer, 1971). More severe pathological changes occurred in the gill epithelium of juvenile steelhead trout than in spring Chinook salmon (Wedemeyer and Yasutake, 1973). Recovery after exposure of 200 μl/l of formalin for 1 hour took 24 hours for the steelhead while the Chinook recovered in a few hours. Widespread hemorrhage of gill lamellae was probably the result of increased blood pressure (Fromm and Olson, 1973).

Little data has been encountered concerning formalin toxicity to fish eggs. Most work deals with trout eggs and is inconclusive and incomplete. (Summary of the available literature is presented in Table 43.) Apparent toxicity begins to occur above 3300 μl/l in 15-minute exposures. Cline and Post (1972) reported toxicity at 300 μl/l in a 1-hour exposure. Astakhova and Martino (1968) used concentrations of 500, 1000, 5000 μl/l of formalin to control fungi on sturgeon, beluga, and Russian (Caspian) sturgeon eggs. Some teratogenic activity occurred in the embryos but the exposure concentration was not indicated. Data was unavailable concerning temperature, duration of exposure and number of eggs affected.

Table 43. Toxicity of Formalin to Fish Eggs (Schnick, 1973)

Eggs of Fish	Toxic concentration	Exposure	Dose (µl/l)	Temp. (°C)	Percent formalin	Reference
Steelhead eggs	LC0	15 min	3,330 (ppm)	--	37	Wold, 1971
Rainbow Trout eggs	Nontoxic	15 min	1,000-2,000 (1:1,000-1:500)	3-5	30	Steffans, 1962
Brown and rainbow trout eggs (infected with Saprolegnia)	LC90	1 hr	300 (ppm)	18.2-19.4	37	Cline and Post, 1972
Brook trout eggs	Some toxicity	15 min	4,000(1:250)	--	37	Reddecliff, 1960
Goldfish eggs	LC	15-30 min	10,000 (ppm)	--	37	Estes, 1957

2. **Amphibians**

Hatchery biologists at the Tishomingo National Fish Hatchery, Tishomingo, Oklahoma, found that 275 to 325 μl/l of formalin produced 20 to 30 percent mortalities among 75 to 100 mm bullfrog tadpoles in 48 hours (Division of Fish Hatcheries, 1969a). Most of the surviving tadpoles became immobilized enough to be captured easily. The larvae of the tiger salamander (*Ambystoma tigrinum*) when exposed to 100 μl/l of formalin for 72 hours were not adversely affected (Helms, 1964). 100% mortality of leopard frog (*Rana pipiens*), toad (*Bufo sp.*) and 25 to 50.8 mm and 102 mm bullfrog (*Rana catesbeiana*) tadpoles were reported with 30, 50, 40 and 80 μl/l of formalin respectively, in 15-gallon aquaria over a 72-hour interval (Helms, 1967; Bennett, 1971; Kemp *et al.*, 1971).

3. Invertebrates

Nazarenko (1960) tested the effects of formalin on two generations of water flea (*Daphnia magna*). Concentrations of 54 μl/l (20 mg/l formaldehyde) of formalin or more were toxic to the Daphnia. In concentrations as low as 13.5 μl/l, Daphnia still exhibited increased mortality. LC50 was reported to lie between 270 μl/l and 2700 μl/l (100-1000 mg/l formaldehyde) when tested in a medium of Reference Dilution Water (Dowden and Bennett, 1965). The median threshold effect for daphnia in 48-hours at 23°C was 5.4 μl/l of formalin (McKee and Wolf, 1971).

Lockhart (1971) performed an evaluation of the effectiveness of formaldehyde in killing nematodes in peat. A 37% formaldehyde solution at the rate of 5 ml per ft^3 freed peat from saprophytic forms of *Panagrolaimus* sp., *Plectus* sp., *Seinura* sp. and *Ditylenchus* sp.

Persson (1973) studied the effects of formalin on egg viability and infective larvae motility of *Ostertagia ostertagi* and *Cooperia oncophora*, both serious cattle parasites. Formalin was tested in concentrations of 0.1%, 0.5%, 1.0%, 2.0% and 5.0%. No effects on eggs or larvae was obtained with 0.1% and 0.5% solutions. With a 1.0% solution, the eggs were destroyed immediately but the larvae were not affected. Only with a 5.0% solution was there a satisfactory effect. However, the necessary concentration would have a negative effect on the germination and growth of crops grown on soil manured with this substance.

Helms (1964) reported no effect on crayfish (*Procambarus blandingi*) even at a concentration of 100 µl/l of formalin for 12 to 72 hours with water temperature ranging from 16°C to 29.4°C.

4. Microorganisms

Formaldehyde has long been known for its toxic effects on microorganisms. As a result of this toxicity, formaldehyde has found many uses as a bacteriocide, fungicide, and a general fumigant. Several studies involving formaldehyde and its ability to destroy bacteria and fungi have been reported in the literature. The results of these studies are described below.

a. General Effects of Formaldehyde on Microorganisms

Neely (1966) observed certain biochemical events that occurred when a population of *Aerobacter aerogenes* was treated with a sub-lethal dose of formaldehyde (50 µg/ml). During the bacteriostatic period there was a change in the base ratio of non-ribosomal RNA and the appearance of induced enzymes capable of metabolizing the formaldehyde at an increased rate. As soon as the formaldehyde concentration had been lowered by metabolism, growth of the colony resumed and the base ratio of non-ribosomial RNA returned to a normal value.

It has been reported that the introduction of 0.75% formalin and 1% potassium permanganate into the nutrient medium stops growth of the root fungus Fomitopsis annosa (Cherykh 1974). A lower concentration of these reagents inhibits vital activities of the fungus; accumulation of biomass decreases; activity of the enzymes - polyphenoloxidase, peroxidase and catalayse drops.

Karpukhin et al. (1973) studied the effects of some solvents and formaldehyde on activated sludge respiration during biochemical sewage treatment. Formaldehyde was the most toxic substance recorded (unknown concentration). Its presence in sewage may markedly deteriorate the process of biochemical sewage treatment. However, certain bacterial species isolated from activated sludge treating industrial wastes from the production of polyester fibers were found to utilize formaldehyde (Grabinska-Loniewska, 1974). Primarily Pseudomonas sp. were able to assimilate the intermediate products of methane and methanol oxidation - formaldehyde and formate.

b. Formaldehyde as a Fumigant

Formaldehyde has found wide use as a fumigant especially in poultry houses. Its fumigation properties as a function of relative humidity have been studied by Hoffman and Spiner (1970). They found that the highest level of formaldehyde residue on surfaces was observed at a relative humidity of 83%. The death rate of microorganisms on exposed surfaces was high for one hour after exposure but decreased rapidly thereafter.

A comparison was made of the relative sensitivity to formaldehyde of the predominant fungi from broiler house litter by treating conidia with aqueous solutions of formaldehyde for 45 minutes at 20°-22°C. Aspergillus sydowi and A. versicolor were most tolerant followed by A. repens, A. flavus, and A. candidus. Least tolerant were Scopulariopsis brevicaulis, A. ruber, A. chevalieri and Penicillium crustosum. Exposure to 2 ppm of formaldehyde for 24 hours killed 99.99% of the spores from pure cultures (Dennis and Gaunt, 1974) but the reduction of viable cells in the dust samples was not so pronounced at this concentration. This failure to achieve a high degree of disinfection of the dust probably resulted from the inability of formaldehyde to penetrate into materials of this kind. In practice paraformaldehyde is used to reach a concentration of 2 to 3 ppm formaldehyde which can disinfect clean surfaces of broiler houses effectively. Dust layers 1 mm or more will not be effectively disinfected and have been shown to have a high microbial population both before and after fumigation with 2 ppm formaldehyde (Dennis and Gaunt, 1974).

Formaldehyde has been applied extensively for routine fumigation of hatching eggs undergoing incubation and of empty incubators. The bacterial flora on the surface of the egg can infect and kill the developing embryo before hatching or the chick after hatching, or they may lower hatchability. Brown and white-shell chicken hatching eggs were given formaldehyde preincubation fumigation for 20 minutes with 1.2 ml of formalin added to 0.6 g of potassium permanganate per cu. ft., and fumigant levels up to 5 times this amount. All levels destroyed the bacteria on the egg surface almost equally (up to 99.85% of bacteria killed). It was observed that more bacteria were killed on the brown-shell eggs (Williams, 1970).

Formaldehyde acts upon the egg surface and the gas does not penetrate to any great extent under the shell or into the albumen of the egg. No residual bactericidal effect on the shell is provided, for the formaldehyde is gone from the shell surface in approximately 2 hours at room temperature (Williams and Siegel, 1969).

Paraformaldehyde flakes which decompose slowly and spontaneously into formaldehyde gas were incorporated into built-up poultry litter at 1 and 3% levels. The treatments had no significant effect on growth weight, feed efficiency or mortality of the chicks. Bacterial counts were reduced to about 10% of control values and mold counts were reduced to about 1% for up to 3 weeks (Veloso et al., 1974).

5. Mutagenic Studies

Rapoport (1946) reported the induction of mutations in Drosophila larvae (by the ClB dominant lethal test) fed formaldehyde, hexamethylenetetramine and salts which liberated formaldehyde. This finding was supported by studies of Kaplan (1948) and Auerbach (1949). However, Auerbach (1949) also showed that formaldehyde was not mutagenic to Drosophila when supplied as a vapor. She postulated that some reaction product or reaction form of formaldehyde was found in the food when formaldehyde was added. This reaction product was believed to be responsible for the mutation.

Mutagenic effects of formaldehyde have also been found in bacteria and fungi (Auerbach and Ramsay, 1968). Demerec et al. (1951) have shown the reversion of streptomysin dependent E. coli to wild type. This is a special mutant in that the alterations may be due to Resistance Transfer Strain Factors rather than genomic constitution. The bacteria were not treated in the medium but in distilled water, and were washed before plating. Auerbach's hypothesis that a formaldehyde-media reaction product is responsible for the mutations is thus not supported by this study. Mutagenicity in Demerec's system was observed at doses which allowed 50% survival of formaldehyde treated bacteria. Englesberg (1952) has also shown mutation in Escherichia coli and Pseudomonas fluorescens. The latter was tested for the ability of formaldehyde to produce mutations at the I locus, allowing the mutant to utilize itaconic acid as the sole carbon source for growth. E. coli B/1 was tested for the induction of resistance to infection by phage T_1. There was some indication in these studies that the effects of formaldehyde could be reversed by the media. A variety of media yielded different viable counts with the same suspension of formaldehyde treated bacteria, but they yielded similar viable counts with an untreated bacterial suspension. This observation may be related to the mechanism of action of formaldehyde and suggests that the formaldehyde reaction is reversible by media components.

Phenotypic delay, a time lag between treatment and recovery of viable mutations, was also found in both Pseudomonas and E coli systems. This lag usually encompassed several division cycles and is thought to reflect a requirement for DNA replication or the formation of a product before the mutation can be expressed. In the case of E. coli phage resistance, the phenotypic delay encompassed six division periods.

Rosenkranz (1972) also studied formaldehyde effects on E. coli B/r in a special mutant lacking a DNA polymerase (pol A^-) and, therefore, a repair deficient strain. Formaldehyde treatment of pol A^+ and pol A^- strains showed differential toxicity, determined by the "zone of inhibition" surrounding a formaldehyde-soaked disc placed on the surface of the growth agar. There was a preferential inhibition of growth in the pol A^- strain, indicating that some repair capability may affect the survival of formaldehyde treated bacteria.

Nishioka (1973) found formaldehyde to be mutagenic in E. coli B/r strains which were altered in another repair function, Hcr^-. This strain lacks the ability to reactivate phage containing UV-induced thymine dimers because it lacks an excision function. Strains of E. coli B/r which were Hcr^- showed more mutation to streptomycin resistance or to tryptophan independence than did the repair competent Hcr^+ strain. Ultraviolet inactivation of Hcr^+ strains was enhanced by treatment with formaldehyde, possibly indicating some effect of formaldehyde on the repair function.

A recent work by Ghora (1974) using high doses of formaldehyde found no mutagenic activity in the mold Chaetominum aureum. However, he was observing only plaque size mutations and discounted, for unexplained reasons, several morphological mutants which were observed. These were neither isolated nor characterized as true mutants and his study is inconclusive.

It is clear that formaldehyde is mutagenic in several types of bacteria and fungi but this effect may be reversible. Reversibility has been found by Zasukhina et al. (1973) for the reactivation of an RNA containing virus, previously inactivated by formaldehyde. The reactivation occurred in the host cell and was suggested to be a spontaneous reversal of the formaldehyde combination with viral nucleic acid.

The reactivation of viral and bacterial products affected by formaldehyde is related to the mechanism of action of formaldehyde. It was first reported by Hoard (1960) that formaldehyde reacts with the free amino groups of polynucleotides in a stoichiometric fashion (1:1) under high formaldehyde concentrations *in vitro*. Haselkorn and Doty (1961) have investigated the interaction of formaldehyde with synthetic polynucleotides and have confirmed the interaction of formaldehyde with free amino groups. They also observed changes in the helical configuration and stability of synthetic poly A-poly U. Haselkorn and Doty confirmed previous models of formaldehyde interaction which proposed a two stage reaction with ribonucleotides. The first stage involves rapid denaturation due the rupture of hydrogen bonds. The second, slower reaction involves the reaction of formaldehyde with free amino groups. They also found that the chemical reaction of formaldehyde with amino groups was completely reversible by heating, without any apparent damage to the integrity or stability of the polynucleotide.

In numerous studies, formaldehyde has been found to combine with RNA or its constituent nucleosides. Alderson (1960a) has found that elimination of yeast RNA from the defined growth medium decreases the effect of formaldehyde on Drosophila mutagenesis through the feeding method. He was later able to reproduce the mutation pattern by reacting RNA or adenosine with formaldehyde at high temperatures before the addition of the mixture to the medium (Alderson 1960b). He found two products of this reaction, a monohydroxymethyl derivative and a dihydroxmethyl derivative of adenylic acid (Alderson 1964). By adjusting his reaction mixtures to produce more of one or the other of these products, he found that the monohydroxymethylation products of RNA or AMP when added to larval medium produced 2.6% sex linked recessives while the dihydroxymethylation products showed percentages not significantly altered above controls (0.3%).

In concurrence with the foregoing studies, formaldehyde has been found to combine more readily with single stranded polynucleotides such as replicating DNA (Voronina, 1964) or synthetic poly A (Filippova *et al*, 1967). The reaction products may also include condensation products of adenosine such as methylene bis AMP. The possibility of formation of these compounds *in vivo* has led to the postulation that adenine dimers may be found in polynucleotides *in situ* or may be erroneously incorporated into polynucleotides (Alderson, 1960b; Filippova *et al*., 1967).

An alternative mechanism of action for formaldehyde has been proposed by Auerbach. This mechanism involves the formation of peroxidation products by autooxidation of formaldehyde or by its reaction with other molecules to form free radicals. In 1968 Auerbach and Ramsay studied the synergism between hydrogen peroxide and formaldehyde in producing mutations in *Neurospora*. The combination of formaldehyde and H_2O_2 was found to be differentially mutagenic at two loci, adenine and inositol utilization. These two loci showed divergent dose response curves when similarly treated with formaldehyde and H_2O_2. This was taken as evidence for a mutagenic peroxidation product.

In a review, Sobels (1963) explains that this combination of H_2O_2 and formaldehyde did not produce more mutations in Drosophila than did formaldehyde alone. The failure of the combination to increase mutation was attributed to a high catalase content in the body tissues enabling the organism to break down peroxides. HCN pretreatment (which inhibits catalase among other enzymes) does increase the mutagenic activity of formaldehyde-H_2O_2 combination causing mutations in previously resistant females and stored sperm in inseminated females. These same targets are effected by dihydroxymethylperoxide, a reaction product of H_2O_2 and formaldehyde. It thus appears that a free radical or peroxide mechanism may be involved in the mutagenic activity of formaldehyde. However, no further studies have been conducted to determine the formation of reactive formaldehyde products in vivo. Additionally, it is not known what other effects may be due to HCN, especially inhibition of repair and respiration.

No cytogenetic evaluation of formaldehyde treated Drosophila have been reported. However, Sentein (1975) reported the destruction of astral and spindle fibers of amphibian eggs exposed to formaldehyde. He noted no effect on the chromosomal complement although cell division was halted.

It is evident that formaldehyde is mutagenic in several species of bacteria and fungi, including strains which are currently used to determine potential hazards of chemicals to man (see carcinogenesis section). The only lukaryote which has been studied in the context of formaldehyde mutation is Drosophila. Here there is a definite effect of formaldehyde on the induction of dominant lethals and sex-linked recessive lethals in larvae which ingest formaldehyde supplemented medium. These results are not duplicated by vapor treatment. However, it is important to note that the mechanism of action of formaldehyde may involve two aspects in which man may differ from Drosophila;

firstly repair capability and secondly metabolism of formaldehyde or formaldehyde condensation products. Both of these aspects have been alluded to in several studies but none have been investigated. Mammals may repair alkylation damage to DNA more efficiently. Also, some methylators of DNA are not dangerous (MMS) while others are highly mutagenic (DMN) probably because of body repair ability. Also, because of its high reactivity, formaldehyde is detoxified in the liver and the erythrocytes and thus not distributed to the gonads where it could be mutagenic. Other organs would not be in danger of mutagenesis by exposure to formaldehyde but the carcinogenic potential of formaldehyde may be suspected due to its mutagenicity and reactivity in bacterial systems.

G. Plants

1. Metabolism

Limited specific data was encountered concerning formaldehyde metabolism in plants. Doman et al. (1961) have shown by the use of ^{14}C tracing that kidney bean and barley plants can absorb gaseous formaldehyde through their leaves. The activity from formaldehyde first appears in phosphate ester fractions followed by alanine, serine, aspartic acid, and unidentified products. Several intensely radioactive unidentified products were detectable in experiments conducted in the dark.

^{14}C-labeled formaldehyde metabolism in 12 day old maize seedlings was studied with and without light. Formaldehyde was oxidized to formic acid which was subsequently oxidized to CO_2 or metabolized to cellular constituents (Zemlianukhin et al., 1972).

2. Toxicity

Nazarenko (1960) studied the effects of formalin on *Aukistrodesmus falcatus* and *ceratophyllum demersum*, a protococcal alga and a hornwort, respectively. A change in the weight and appearance of the hornwort were used as indicators of the effects of formalin. A slight drop in weight was noticed at 2.7 μl/l of formalin (1 mg/l of formaldehyde). A concentration of 13.5 μl/l of formalin (5 mg/l of formaldehyde) or greater caused an 80% or more reduction in weight after 20 days exposure. Concentrations of 13.5 μl/l of formalin (5 mg/l formaldehyde) or greater adversely affected the color and number of cells of the alga after 18 days exposure (Nazarenko 1960, van Duijn 1967).

Helms (1964) tested formalin against seven genera of algae in a series of quart jars containing an alga and 5 to 100 μl/l (ppm) of formalin. After 7 days, no adverse effects were detected for *Aphanothece*, *Oscillatoria*, and *Rhizoclonium* exposed to 100 μl/l (ppm) of formalin but *Scenedesmus*, *Sirogonium*, *Spirogyra*, and *Stigeoclonium* died at concentrations between 15 and 50 μl/l (ppm).

Koning and Jegier (1970) performed experiments concerning formaldehyde effects upon photosynthesis and respiration of *Euglena gracilis*. Air containing 0.075 ppm of formaldehyde was passed through 5 ml of *Euglena* sample for one hour at a flow rate of 90 ml/min. Photosynthesis was measured by the rate of O_2 evolved during daylight plus 3000 foot-candles. Respiration was measured by the rate of O_2 absorbed in the absence of light. *Euglena* cells exposed to 0.075 ppm of formaldehyde for one hour showed a lowered rate photosynthesis and respiration. However, only the change of the rate of respiration approaches statistical significance. It appears that Euglena cells are injured only slightly to exposure of formaldehyde under the given experimental conditions.

3. Mutagenicity

Loveless (1951) reported that after one hour of exposure of Vicia faba root tip meristems to a wide series of unspecified formaldehyde concentrations, no "radiomimetic" behavior was detected. However, a low incidence of chromosomal breakage was observed after subjection to sub-lethal concentrations of dihydroxymethyl peroxide. It was suggested that the mutagenic activity of formaldehyde may act through the intermediate formation of organic peroxides by reaction with naturally produced hydrogen peroxide. It is suspected that the activity of organic peroxides is due to their ability to liberate alkyl radicals.

Avakyan and Amirbekyan (1968) observed a "significant increase" in the meristem of primary radicals of Vicia faba subjected to 2 hours exposure of formalin (40% formaldehyde) at a concentration of 1:100. At a concentration of 1:10 there was a nominal decrease in the percentage of chromosomal rearrangements and at a concentration of 1:300 there was no significant difference from the control plants.

V. REGULATIONS AND STANDARDS

A. Current Regulations

No regulations or standards concerning formaldehyde in food or drugs were uncovered in the literature. Personal contacts with these authorities confirmed that no written enforcable standards exist. However, according to these contacts "it is unlawful to have formaldehyde in food."

Tolerances for residues of fungicide formaldehyde in or on agricultural commodities have been exempted by the EPA (1975a) when such commodities are used for animal feed. These feed commodities consist of grains of barley, corn, oats, sorghum and wheat and forages of alfalfa, Bermuda grass, bluegrass, broml grass, clover, cow pea hay, fescue, lespedeza, lupines and numerous other grasses.

Formaldehyde has been given a "C" rating in the EPA categories for Harmful Quantity Determination (EPA, 1975b). This category includes substances which are:

(1) slightly toxic to aquatic life (Rating 2) or

(2) cause a serious reduction of amenities being highly objectionable due to smell, persistency, poisonous or irritant characteristics (Rating XXX) or

(3) are practically non-toxic to aquatic life (Rating 1) but moderately hazardous to human health (oral intake, Rating 3 or 4) and causing moderate reduction of amenities (Rating XX).

Category "C" substances have LC50 values of 10 ppm up to 100 ppm. LC50 is the concentration of material lethal to one half of the test population of aquatic animals when continuously exposed for 96 hours to the test substance.

A harmful quantity of 100 lbs (45.4 Kg) has been assigned to formaldehyde by the EPA. This is the amount of formaldehyde considered harmful when it is discharged into drinking water reservoirs, waters of a Natural Wildlife Refuge, National Forest Wilderness, Designated National Park or waters of a National Wilderness Preserve.

Effluents containing formaldehyde are not regulated per se. However they must meet the general effluent guidelines set forth by EPA in pursuant to the Federal Water Pollution Control Act.

Currently there are no OSHA standards for formaldehyde. However, the Manufacturing Chemists Association has listed formaldehyde as one of the chemicals to be studied.

B. Consensus and Similar Standards

The American Conference of Governmental Industrial Hygienists (1974) have established threshold limit values (TLV) for formaldehyde. The TLV is currently 2 ppm at 25°C and 760 mm Hg pressure or 3 mg/m^3 of air. This value (2 ppm) is a ceiling value ("C" value) that should not be exceeded, or is considered to be the maximum allowable concentration (MAC). The assigned "C" limit indicates that an excursion above the MAC (2 ppm) for a period up to 15 minutes may result in intolerable irritation, chronic or irreversible tissue damage, or narcosis of sufficient magnitude to increase accident proneness, impair self rescue or reduce work efficiency. The current Russian standard for formaldehyde air pollution permissible for work environments is 1.0 mg/m^3.

VI. EVALUATION AND COMMENTS

A. SUMMARY

Formaldehyde is a high volume chemical in the United States. Production levels are currently approximately 6000 million pounds annually on a 37% basis. The demand for formaldehyde as a raw material for resins production and chemical synthesis is expected to continue to increase, with production levels forcasted to reach 7600 million pounds by 1979. Currently, 77.1% of the formaldehyde manufactured in the United States is produced by the silver catalyst process, 22.9% by the metal oxide process. The major emissions from both of these processes are from the absorber vents. In the silver catalyst process, the absorber vent tail gas is rich in hydrogen and CO. Many plants are currently feeding this stream to the boiler furnace, thus cutting fuel costs. This pollution abatement procedure has proved to be highly economical, with rates of return on the equipment investment of up to 45% annually. In contrast, the absorber tail gases from the metal oxide process do not contain large quantities of combustibles. These gases are currently being exhausted into the atmosphere in most plants. Thus, of the two production processes, the metal oxide catalyst contributes more emissions to the atmosphere.

Most of the formaldehyde produced is for captive use in the production of phenolic, urea, melamine and acetal resins. The environmental contamination from formaldehyde resins manufacture is difficult to assess without a thorough survey of the resins industry, itself. However, the main effluent is water from dehydration processes. The aqueous effluent contains formaldehyde in concentrations dependent upon the type of formaldehyde used as a starting material.

The environmental contamination from formaldehyde manufacture and industrial use is small and localized compared with other sources. Combustion is responsible for most of the formaldehyde entering the environment. The largest source of formaldehyde from combustion is the automobile, which puts over 610 million pounds of formaldehyde into the air over the United States each year. In addition to the formaldehyde, hydrocarbons are also emitted in large quantities. Through photochemical processes in the atmosphere, these hydrocarbons are oxidized to formaldehyde, etc., further adding to the pollution from this compound.

Natural mechanisms exist for degradation of formaldehyde. In the atmosphere, photochemical degradation to CO_2, CO, H_2O, H_2O_2, etc. occurs. In aqueous and soil media, bacteriological degradation serves to oxidize the formaldehyde to CO_2 and water, or incorporate it into cell mass. This process is accomplished by certain methylotrophic bacteria which can utilize formaldehyde as a carbon source.

Formaldehyde is toxic to most forms of life. Its main toxic action is that of protein coagulation. Inhalation toxicity is manifested by lung hemorrhages and edema, respiratory collapse and death. Ingestion of concentrated solutions results in severe gastointestinal tract damage, and liver and renal damage. In subacute exposures, formaldehyde has been shown to cause lung irritation, central nervous system depression, and dermatitis on contact with the skin. Inhalation of doses of less than one ppm are reported to cause central nervous system response suggesting that the current TLV of 2 ppm for industrial exposure is too high.

Even though it is relatively toxic, formaldehyde is a normal metabolite in most animal systems. As such, the body can efficiently use or detoxify small quantities of this compound. Liver and erythrocytes have the enzymes for oxidation of formaldehyde to formic acid. Further oxidation to CO_2 and water can occur, or formate can enter the one carbon pool or be eliminated by the kidneys.

In contrast to formaldehyde, hexamethylenetetramine appears to be relatively innocuous. It is readily absorbed by the gastrointestinal tract and passes through the body unchanged and is eliminated in the urine. When the urine is acidic, hexamethylenetetramine breaks down into ammonia and formaldehyde which is the basis for its use as a urinary antiseptic.

Formaldehyde is a known mutant in bacteria and Drosphila. It has been shown to produce mutations in bacterial strains which are thought to be relatively reliable test strains for indicating potential carcinogenicity. Several carcinogenicity studies with both formaldehyde and hexamethylenetetramine have been conducted. Carcinogenic response was observed with repeated subcutaneous administration (Watanabe). However, Watanabe's studies appear to be highly questionable for two reasons:

- lack of control comparison
- repeated subcutaneous injections at the same site are known to produce cancers, even when the compound being injected is not a carcinogen.

Most of the negative studies have not used sufficiently high dosages and/or sufficiently long observation periods.

Mutagenic or teratogenic behavior also has not been observed with formaldehyde or hexamethylenetetramine in animal studies. However, occupational studies on Russian women exposed to formaldehyde-urea resin did indicate increased complications in pregnancy and underweight children. Metaldehyde, an analog of trioxane, has been shown to have some mutagenic and teratogenic activity. No information on the mutagenic or teratogenic properties of trioxane, itself, has been encountered.

B. CONCLUSIONS AND RECOMMENDATIONS

(1) Formaldehyde is definitely an environmental contaminant. It is present in minor amounts in the atmosphere. Under smog conditions, formaldehyde is one of the main constituents responsible for eye and respiratory tract irritation. The major source of formaldehyde emissions is the automobile.

(2) The manufacture of formaldehyde by the silver catalyst process is almost free of emissions, if the absorber tail gases are burned. The tail gases from the metal oxide process are not combustible resulting in significant releases to the atmosphere. However, this process accounts only for approximately one-fourth of the formaldehyde produced. A study to develop an economical method for elimination of this gas stream is needed to improve local emissions problems.

(3) The formaldehyde resins manufacturing industry and the industrial use of resins result in releases of formaldehyde to local community environments and to the industrial environment.

(4) Russian workers have reported central nervous system response to inhalation of formaldehyde at concentrations below one ppm.

(5) Studies to date have not definitely established the carcinogenic potential of formaldehyde. Well-controlled, life-time studies are needed to resolve this question.

(6) The mutagenic-teratogenic properties of metaldehyde lends some suspicion to trioxane. Multiple generation studies with trioxane are needed to fill this information gap.

(7) Bis(chloromethyl)ether (BCME) has been shown to be a human carcinogen. However, it is rapidly hydrolyzed to HCl and formaldehyde upon contact with water. The same reaction would be expected with lung tissue raising the question as to the actual carcinogen, BCME or its hydrolysis products. Further information could be obtained by a controlled comparison using the following test matrix:

- exposure to bis(chloromethyl)ether
- simultaneous exposure to HCl and formaldehyde levels equal to those predicted from the ether hydrolysis.
- alternate exposure to formaldehyde and HCl.

(8) Sodium chloride aerosols have been shown to potentiate the effect of formaldehyde on the organism. However, under real life conditions, aerosols are not usually inert. Therefore, synergistic studies with aerosols such as sulfuric acid, ammonium sulfate, and other components of photochemical smog are needed.

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